EFFICACY OF TACROLIMUS IN CHILDREN WITH STEROID-DEPENDENDENT (SDNS) AND STEROID-RESISTANT NEPHROTIC SYNDROME (SRNS)

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I hereby declare that the thesis entitled **"EFFICACY OF TACROLIMUS IN CHILDREN WITH STEROID-DEPENDENT (SDNS) AND STEROID-RESISTANT NEPHROTIC SYNDROME (SRNS)**" submitted towards partial fulfillment of the requirements for the award of **MD in PAEDIATRICS** degree to BFUHS is a compilation of original work carried out by me under the supervision of **Dr. Gurdeep Singh Dhooria** Professor, Department of Paediatrics, **Dr. Deepak Bhat**, Professor, Department of Paediatrics, DMCH, Ludhiana. No part of this thesis has formed the basis for the award of any degree previously.

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Dedicated

to

My Parents

Friends,

&

Teachers

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LIST OF ABBREVIATIONS

AKI	Acute Kidney Injury
AUC	Area Under Curve
CNIs	Calcineurin Inhibitors
CRI	Chronic Renal Insufficiency
CR	Complete Remission
CRNS	Corticosteroid Resistant Nephrotic Syndrome
CSNS	Corticosteroid Sensitive Nephrotic Syndrome
CsA	Cyclosporine
ESRD	End-Stage Renal Disease
FSGS	Focal Segmental Glomerulosclerosis
FR	Frequently Relapsing
FRNS	Frequently Relapsing Nephrotic Syndrome
INS	Idiopathic Nephrotic Syndrome
ISRNS	Idiopathic Steroid Resistant Nephrotic Syndrome
ISA	Immunosuppressive Agent
ISKDC	International Study For Kidney Disease Of Children
IVCP	Intravenous Cyclophosphamide
MPGN	Mesangioproliferative Glomerulonephritis
MCD	Minimal Change Disease
MMF	Mycophenolate Mofetil
NS	Nephrotic Syndrome
NR	Non Remission
PR	Partial Remission
PSL	Prednisolone
PMLE	Progressive Multifocal Leukoencephalopathy
RCTs	Randomized Control Trial
SR	Steroid Resistant
SRNS	Steroid Resistant Nephrotic Syndrome

SS	Steroid Sensitive
SSNS	Steroid Sensitive Nephrotic Syndrome
TAC	Tacrolimus
TR	Total Remission
TW	Tripterygium
UTI	Urinary Tract Infection

ABSTRACT

Title: Efficacy of Tacrolimus in Children with Steroid-Dependent (SDNS) and Steroid-Resistant Nephrotic Syndrome (SRNS)

Introduction: Nephrotic syndrome (NS) is a common renal disorder in children, and it can be classified as steroid-dependent (SDNS) or steroid-resistant (SRNS). Tacrolimus (TAC), an immunosuppressive drug, has been used to manage NS. This study aimed to evaluate the efficacy and safety of tacrolimus in children with SDNS and SRNS.

Methods: This retrospective study enrolled 43 children who met the inclusion criteria. The patients were divided into SDNS (n=22) and SRNS (n=21). The study collected data on patient demographics, clinical characteristics, previous treatments, and laboratory parameters. The primary outcome was the proportion of patients achieving complete remission (CR) after 6 and 12 months of tacrolimus treatment.

Results: The median age of the study participants was 3.8 IQR (2-5) years. The median number of relapses in SDNS before TAC and after starting TAC was 3 IQR (1-4) and 0 IQR (0-2.0), respectively (p-value <0.05). At 6 months, complete remission (CR), partial remission (PR) and no remission (NR) were seen in 86.4%, 9.1% and 4.5% of patients with SDNS respectively and 42.9%, 14.3%, and 42.9% of patients with SRNS, respectively. A total of 95.5% of patients in SDNS and 57.2% of patients with SRNS were responders (CR+PR). The median-dependent dose in SDNS before and after treatment with tacrolimus (TAC) were 1.4 (1.23-1.5) and 0.55 (0.45-0.93) mg/kg/day, respectively. The median steroid dependent in SRNS after one year of tacrolimus was 0.8 mg/kg/day. Eight patients with SDNS and two patients with SRNS were put off steroids for ≥ 6 months.

Conclusion: TAC treatment achieved CR in both SDNS and SRNS patients, with a higher response rate observed in SDNS patients. Tacrolimus was well-tolerated, and adverse effects were generally mild and manageable.

Keywords: Nephrotic syndrome, tacrolimus, steroid-dependent,steroid-resistant, complete remission.

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INTRODUCTION

Nephrotic syndrome is a common glomerular disease in childhood, with most cases being idiopathic. The cause of this disease is not yet fully understood, and classification is based on several factors, including responsiveness to steroid treatment, relapse tendency, histopathological findings, and gene mutations.

Nephrotic syndrome is characterized by massive proteinuria that causes hypoalbuminemia and leads to hyperlipidemia, edema, and other consequences. Increased permeability through the renal glomerulus damaged basement membrane is the reason. [1]

Lab Parameters to diagnose nephrotic syndrome: [2]

Serum albumin	< 3.0 g/dL
Proteinuria	40 mg/m2/h or > 1000 mg/m2/day; spot Up/Uc >2 mg/mg; 3-4+ by dipstick
Hyperlipidemia	Increase in cholesterol or triglycerides

The incidence of idiopathic nephrotic syndrome (INS) is approximately 1–3 per 100,000 children, and its prevalence is 16/100,000 in children below 16 years of age, male to female ratio being 2:1 in nephrotic syndrome. [3]

The two broad classifications of idiopathic nephrotic syndrome are steroid-sensitive (SS) and steroid-resistant (SR), which guide treatment decisions but do not provide insights into the disease mechanism. The main component affected in this disease is the podocyte, and it is thought that some immune mechanism may be involved based on the response to corticosteroids.

Steroid-sensitive nephrotic syndrome (SSNS) is characterized by complete remission within six weeks of treatment with prednisolone at 60 mg/m2/day (2 mg/kg/day; maximum 60 mg/day). Failure to achieve complete remission after six weeks of steroid treatment is classified as steroid-resistant nephrotic syndrome (SRNS). [4]

INS is the most common nephrotic syndrome in children accounting for nearly 90% of children with nephrotic syndrome. Minimal change nephrotic syndrome (MCNS) is INS's most common type. With MCNS, the child usually has relapses of the illness, but the disease can generally be managed, and the prognosis is typically good. In rare cases, a child may develop kidney failure that requires dialysis.

Congenital nephrotic syndrome is a rare nephrotic syndrome presenting in the first three months of life. It is inherited by an autosomal recessive gene, meaning that males and females are equally affected. The child inherits one copy of the gene from each parent, who are carriers. The chance for carrier parents to have a child with congenital nephrotic syndrome is one in four, or 25 percent, with each pregnancy. The outcome for this type of nephrotic syndrome is inferior. [5]

INS usually begins between 2 and 8 years of age with puffiness of the face in the morning, progressing to generalised edema. Edema progresses to the abdominal wall, sacral region, genital, and lower limbs. In severe cases, it may involve the scalp and form ascites and pleural effusion. It may be associated with infection. Blood pressure may be elevated transiently in 10–15% of steroid-sensitive nephrotic syndrome (SSNS). Initially, parents and family physicians may consider good weight gain due to improved health or allergy as the cause of a chubby face. Diagnosing nephrotic syndrome can be easily diagnosed by bedside urine examination using a dipstick, demonstrating heavy proteinuria (3+ to 4+). [6] Urine microscopy may reveal microscopic hematuria in 20–25% of cases of MCNS. Persistent microscopic hematuria is common in FSGS or mesangial-proliferative

glomerulonephritis (MPGN). [6,7] Hospitalization is warranted in some patients of INS with edema and ascites causing respiratory distress, hypovolemia, and oliguria. Abdominal pain due to peritonitis, hypovolemia, pancreatitis or gastroenteritis, and urinary tract infection (UTI). Serious infections, like bacterial peritonitis, pneumonia, septicemia, cellulitis, or meningitis, can be the initial presentation during the first attack or relapse.

Steroid therapy is the mainstay of treatment for all children with INS, regardless of their histopathologic type, including FSGS. Since most children with nephrotic syndrome respond to steroids, a trial of steroid therapy without a prior biopsy is warranted. [6-9] Prednisolone is the drug of choice and has been used by the International Study for Kidney Disease of Children (ISKDC) for over 60 years. Although the mechanism of action of prednisolone in nephrotic syndrome is unclear, its efficacy in treating autoimmune disorders is well-established. Prednisolone's anti-inflammatory effect may reverse increased capillary permeability and suppress polymorphonuclear neutrophil activity, thereby reducing proteinuria in nephrotic syndrome. Deflazacort, a new steroid, is not recommended as initial therapy at this time. The primary goals of INS treatment are to minimize steroid toxicity, stop proteinuria as soon as possible, and prevent relapse. The following steroid therapy protocol is currently recommended for initial therapy: oral prednisolone at a dose of 2 mg/kg or 60 mg/m²/day (maximum 60 mg) in 2-3 divided doses for six weeks. About 90-93% of patients respond to this regimen within 10-15 days, and an additional 3% enter remission when prednisolone is given at a dose of 1.5 mg/kg or 40 mg/m² as a single dose on alternate days for six weeks. A 12-week course is recommended for the first attack, as it has been found to reduce the relapse rate by 25-30% compared to an 8-week treatment and is therefore preferred. [8,9]

After treatment with prednisolone, a child undergoes the following.

• Remission/response: Proteinuria less than 4 mg/m²/day or 0-trace on dipstick for three consecutive days

• Resistance: Failure to achieve remission in 4–6 weeks of daily prednisolone therapy

• Relapse: Recurrence of proteinuria more than 40 mg/m² or 50 mg/kg/day or urine albumin 3+ to 4+ on dipstick on three consecutive days after previously being in remission or uPCR more than 2 in a spot sample

• Frequent relapser: Two or more relapses in 6 months or four relapses within any 12 months

• Steroid dependent: Two consecutive relapses while reducing the dose of prednisolone or within 15 days of stopping or on shifting to A/D

• Early steroid resistance: Steroid resistance during initial therapy

• Late steroid resistance: Steroid resistance in a patient who had earlier responded to corticosteroid therapy.

Steroid Toxicity

Children with steroid-dependent and frequently relapsing nephrotic syndrome often experience side effects due to repeated courses and prolonged high doses of steroids. Daily or lengthy alternate-day therapy can lead to common side effects such as growth retardation and osteoporosis. Steroid-dependent nephrotic syndrome can also result in low 25-hydroxy vitamin D and changes in osteocalcin and alkaline phosphatase levels. Therefore, children who are receiving prolonged steroid therapy are advised to take vitamin D and calcium supplements. Other side effects of steroid therapy include weight gain, cataracts, behavior disturbances, and hypertension. Additionally, cosmetic effects such as hirsutism, striae, and Cushingoid facies are common. The prolonged course of the disease and the patient's

immunocompromised state can also increase the risk of infections, leading to mortality and morbidity in steroid-dependent and frequent-relapsers. Alternate drugs are recommended as steroid-sparing agents to control proteinuria and its ill effects. [9,10] Growth failure can also result from nephrotic syndrome, which can be caused by prolonged corticosteroid therapy, the nephrotic state, protein malnutrition, and hypothyroidism.

Many patients with nephrotic syndrome experience temporary relapses, which typically resolve within 4-14 days. However, around 40-50% of patients who achieve complete remission may still develop relapses or steroid dependence even after a long initial course of steroids.

Treatment of Relapse

In SSNS, relapses are common, with rates of 70-90%. In cases of relapsing SSNS, around 70% of patients relapse frequently and 50-60% experiences a relapse as soon as steroid therapy is reduced or stopped, which is known as steroid dependence. Children under 5 are at a greater risk for relapse, which can pose therapeutic challenges. However, if there is no relapse or persistent remission for a period of 18-24 months after stopping treatment, the patient has likely achieved a definitive cure.

To treat a relapse, daily prednisolone is administered (at a dosage of 2 mg/kg/day) until remission is achieved, followed by four weeks of alternate-day therapy. In cases of frequent relapses or steroid dependence, the ISKDC recommends repeated courses of prednisolone at a dosage of 60 mg/m²/day to produce remissions, followed by 40 mg/m² on an alternate day for an additional four weeks. Slow tapering of prednisolone to a dose of 15-20 mg/m² on an alternate day is recommended for a period of 12-18 months in frequently relapsing or steroid-dependent cases to minimize steroid side effects. This regime effectively reduces relapse risk and does not affect growth velocity, except in the pubertal age group. [9] Respiratory infections may

precede relapses and exacerbate proteinuria during prednisolone therapy. Some studies suggest that daily prednisolone therapy for 5-7 days may reduce relapse risk during upper respiratory tract infections, as opposed to alternate-day treatment.

Nephrotic syndrome resistant to steroid therapy is known as SRNS, identified by the lack of complete remission following six weeks of daily prednisone medication at a dose of 60 mg/m2 per day.
Despite accounting for a smaller proportion of nephrotic syndrome cases, SRNS patients have proven more challenging to treat, with 36% to 50% progressing to end-stage renal disease (ESRD) within ten years. [11]
Current treatments aimed at immunopathogenic mechanisms, such as corticosteroid therapy, alkylating agents, or Calcineurin inhibitors (CNIs), can fail and result in a poor long-term outcome. Evidence suggests that immunosuppressive therapy is generally more effective for children with MCD or secondary steroid resistance than those with FSGS or initial steroid resistance. Corticosteroids are still a crucial part of therapy for NS, given in combination with other agents in steroid-resistant NS, with the dose gradually decreased to alternate days to minimize side effects.

The current guidelines recommend using CNIs in combination with steroids for children with SRNS. CNIs are administered for at least six months and discontinued if partial or complete remission of proteinuria is not achieved by six months. The guidelines also suggest continuing CNIs for one year when partial remission is attained by six months, with low-dose steroids combined with CNI therapy.

Cyclosporine has been found effective in improving the outcome of pediatric patients with SRNS when used in a dose of 150-200 mg/m2 in combination with oral prednisolone. Cyclosporine (CsA) binds cyclophilin and inhibits the production of IL-2 and other lymphokines. SRNS can be successfully treated with CsA therapy, and many children achieve either complete/partial remission. [12,13] A study by the

German Society of Paediatric Nephrology (APN; since 2008, GPN) group suggests it is more efficacious than intravenous cyclophosphamide. [12] Although there was no difference in the number of patients achieving complete remission; those patients receiving CsA treatment were significantly more likely to achieve partial remission than those receiving intravenous cyclophosphamide. However, this therapy has side effects, including hypertension, hyperkalemia, acute kidney injury (AKI), hirsutism, and gum hyperplasia. CsA is also nephrotoxic when used in high doses and for prolonged periods and has been associated with CKD with progressive interstitial fibrosis and tubular atrophy. Thus, monitoring CsA levels during treatment is essential. While CsA therapy has a success rate of 40-50%, relapse after discontinuing the drug is a significant concern. [13,14]

Patients who respond to CsA therapy should be treated for at least 2-3 years, with the dose tapered to the lowest effective dose and maintaining target levels of 75-150 ng/mL for another 1-2 years. However, some patients who respond to CsA therapy may still relapse on discontinuation, and reintroduction of treatment is not always effective. Although there are reports of successful switching from CNI to mycophenolate mofetil, the long-term benefits of this strategy require confirmation. If children have persistent nephrotic range proteinuria beyond six months of treatment, therapy should be considered ineffective and stopped. Those showing complete or partial remission should be treated for at least 2-3 years.

Mycophenolate mofetil (MMF) is a newly developed drug that acts as an immunosuppressant by blocking the production of purines by inhibiting the enzyme inosine monophosphate dehydrogenase, leading to the suppression of T- and B-lymphocyte proliferation. Additionally, it impedes the attachment of activated lymphocytes to endothelial cells by inhibiting the glycosylation of adhesion molecules. However, its effectiveness as a single therapy for SRNS is limited. According to KDIGO (Kidney Disease Improving Global Outcome) guidelines, in

cases where CNI therapy fails to induce remission in children, MMF can be used in combination with high-dose corticosteroids. It is also useful in tapering off CsA therapy in children with SRNS who have become dependent on CsA. [15]

Cyclophosphamide, an alkylating agent, has been utilized in treating both SDNS and SRNS. [16-19] According to current KDIGO guidelines children with SRNS should not receive cyclophosphamide. This recommendation is based on results from the ISKDC study and anecdotal reports indicating that neither oral cyclophosphamide nor chlorambucil improved the outcome of patients with SRNS, as 25% of both the steroid alone and the steroid plus cyclophosphamide groups had a complete remission. However, Geary et al. found that cyclophosphamide resulted in either a partial/complete remission in 48% of study patients with SRNS. They also discovered that the risk of Chronic Renal Insufficiency (CRI) or ESRD was lower in children whose SRNS was cyclophosphamide sensitive.

The efficacy of monthly intravenous cyclophosphamide pulse (IVCP) therapy at a dose of 500 mg/m2 in treating SRNS compared to children who received oral cyclophosphamide, more children in the IVCP group achieved sustained remission, had long periods without proteinuria, and experienced fewer side effects. In Focal Segmental Glomerulosclerosis (FSGS), a similar regimen of IVCP infusions was utilized, but at a higher dose of 750 mg/m^2 along with oral prednisolone, resulting in a response rate of 65%. Results are comparable to Mendoza's protocol of intravenous methylprednisolone, but with a much shorter duration of treatment (6 months), a fraction of the total cost, and minimal side effects. [19]

A single trial has compared intravenous cyclophosphamide with oral prednisone versus oral cyclophosphamide, intravenous dexamethasone, and oral prednisone.[20] Following six months of therapy, in the 45 children, complete remission was achieved in 50% of the IVCP group versus 43% in the oral cyclophosphamide group.

Although the sample size was small, the percentage of children who attained remission with intravenous cyclophosphamide was marginally higher. Most of these studies did not evaluate children for genetic mutations before treatment. An unequal inclusion of children with NPHS2 mutations in treatment groups in Randomized Control Trial (RCTs) could bias the results. Therefore, cyclophosphamide remains a viable treatment option for SRNS due to Minimal Change Disease (MCD). It may have a significant remission rate, restore steroid responsiveness, and is very economical, especially for developing countries. The efficacy of other cytotoxic agents like azathioprine, chlorambucil, and vincristine has been deemed poor.

Rituximab is an anti-CD20 monoclonal antibody that is very effective in these children with steroid-dependent NS. The mechanism of action of rituximab in INS has yet to be discovered. There is downregulation of β-cell receptors, shedding of CD23 cells and apoptosis of CD20+ cells, general regulatory effects on the cell cycle, and increases in MHC II and adhesion molecules LFA-1 and LFA-3 (Lymphocyte Function-associated Antigen). It has been found that 2–4 doses given at an interval of 1–2 weeks can lead to sustained remission in about 50% of these children. [21] As per KDIGO guidelines, there is currently insufficient evidence to recommend rituximab to treat these patients. Moreover, there is a risk of this drug's severe adverse effects, including infusion-related reactions like hypotension, fever, rigors, serious infections, and progressive multifocal leukoencephalopathy (PMLE). In addition, there is a case report of a death associated with rituximab therapy in a child due to lung fibrosis with SRNS. [21] Hence, the routine use of rituximab is not recommended in these children.

Tacrolimus is a calcineurin inhibitor utilized as an alternative treatment option for children with steroid-resistant nephrotic syndrome. It has a more potent cytokine suppression effect than CsA, inhibiting IL-2-dependent T-cell activation. Tacrolimus is absorbed slowly through the gastrointestinal tract, with a bioavailability of 20 to 25%. Tacrolimus is

primarily bound to erythrocytes (95%) in the blood and partially (5%) bound to plasma proteins in the plasma. Foods high in fat delay its absorption, and maximum blood concentration occurs after 2-3 hours of oral intake.

It is metabolized by CYP3A4 in the liver and excreted in the faeces as an inactive metabolite. In healthy people, the biological half-life is around 46 hours, while transplant recipients have a half-life of 12-16 hours. [22]

Tacrolimus has fewer cosmetic side effects than CsA and is typically given at a dose of 0.1 mg/kg/day to achieve a trough level of 5–10 g/L within the first three months of treatment. Several studies have reported success using tacrolimus to induce remission in children with SRNS, including those who have not responded to CsA. In a pilot study, remission in 19 out of 22 children including those who had previously not responded to CsA. [23] Similar results have been reported in several other studies. Gulati et al. compared tacrolimus and cyclophosphamide. Their study showed that tacrolimus and alternate-day steroids led to complete remission in 52.4% of patients. The combined therapy of tacrolimus and steroids was a safe initial treatment option for managing pediatric SRNS. [22]

Consensus Guidelines on Management of Steroid-Resistant Nephrotic Syndrome 2021 suggested of starting dose of tacrolimus 0.1-0.2 mg kg/day in 2-divided doses; maximum initial dose 4 mg/day; trough level 4-8 ng/mL [2]

Jahan et al. showed that SRNS pediatric patients treated with tacrolimus responded up to 80%, with complete remission achieved in 64% of patients and the least adverse effects. While in comparison, this study showed a response rate of 97.4% in patients treated with tacrolimus. [25] However, monitoring tacrolimus levels and renal function is essential as it can be nephrotoxic. In a study comparing CsA and tacrolimus, both drugs effectively managed SRNS, but tacrolimus is cheaper and has fewer cosmetic side effects than CsA. [24] One

downside is that it is only available in capsule form, making it less suitable for use in younger children with SRNS.

In India, there is a paucity of data on the use of tacrolimus in SDNS & SRNS in children; hence, the study was planned.

AIMS AND OBJECTIVES

1. To study the efficacy of Tacrolimus in children with Steroid-Dependent (SDNS) and steroid-Resistant Nephrotic Syndrome (SRNS).
2. To study the safety of Tacrolimus

REVIEW OF LITERATURE

What is nephrotic syndrome?

Sinha et al (2021) According to revised guidelines by ISPN (2021), nephrotic syndrome, characterized by edema, heavy proteinuria (>1 g/m2 daily; >40 mg/m2/hr) and hypoalbuminemia (serum albumin <3 g/dL), is among the most common kidney diseases in childhood. The condition has an annual incidence ranging from 1.2 to 16.9 per 100,000 children. While nephrotic syndrome is usually primary or idiopathic, evaluation might reveal an underlying systemic illness in 5-10% of patients. Kidney biopsy reveals minimal change disease in ~80% patients, and focal segmental glomerulosclerosis (FSGS) and mesangioproliferative glomerulonephritis (GN) in 7-8% each. Therapy with prednisolone results in complete remission of proteinuria in 85-90% patients, termed steroid sensitive nephrotic syndrome (SSNS). While the outcome in patients with SSNS is satisfactory, approximately 50% show frequent relapses or steroid dependence, and 3-10% show late steroid resistance.[25]

Efficacy of Tacrolimus

Segarra A et al (2002) analysed the efficacy and safety of a combined therapy of tacrolimus and steroids in 25 patients with idiopathic primary focal glomerulosclerosis and proven resistance to or dependence on cyclosporin A. After 6 months trial of tacrolimus and steroids, proteinuria decreased in 17 patients (68%) complete remission in 10 patients (40%), partial remission in two patients (8%) and a moderate reduction in proteinuria to levels <3 g/day was seen in five additional patients (20%). The only predictor of response to tacrolimus was a previous response to cyclosporin and prednisone, either as a complete or partial remission (remission rate 75% *vs* 15.3; *P*=0.036). Mean time to remission was 112±24 days. After tacrolimus discontinuation, 13/17 patients (76%) relapsed and were treated with a second trial of tacrolimus for 1 year, achieving complete remission in five patients

(38.4%), partial remission in four patients (30.7%) and reduction of proteinuria <3 g/day in four patients (30.7%). After 2 years of follow-up, 12 patients (48%) were on sustained remission. The main side effect was acute reversible nephrotoxicity (40%). Study concluded that combined therapy of tacrolimus and steroids induce sustained remission of proteinuria in a significant number of patients with idiopathic focal glomerulosclerosis whose disease was not controlled by the standard therapy of steroids and cyclosporin A.[26]

Westoff et al (2006) conducted an open, monocentric, non-randomized, prospective trial where data from 10 patients were taken. Five patients with steroid-dependent minimal-change nephrotic syndrome, 1 patient with steroid-refractory minimal-change disease and 4 patients with steroid-refractory FSGS were started on tacrolimus at trough levels of 5 – 10 µg/l. In case of steroid-dependence, prednisolone was tapered off in presence of tacrolimus within one month. Results: Within 6 months, complete remission was achieved in 5 patients (50%) and partial remission in 4 patients (40%), yielding a final response rate of 90%. One patient was primarily resistant to tacrolimus (steroid-refractory minimal-change), another patient became secondarily resistant to tacrolimus after an initial remission (steroid-refractory FSGS). Average proteinuria significantly decreased by 77% from 9.5 ± 1.4 – 2.2 ± 1.1 g/day (p-value <0.05). Serum protein significantly raised from 55.0 ± 1.9 – 64.6 ± 1.9 g/l (p-value <0.05). Tacrolimus induced non-significant increases of blood glucose (4.9 ± 0.1– 5.1 ± 0.2mmol/l), systolic blood pressure (131.4 ± 7.1 – 139.0 ± 7.6 mmHg) and creatinine (93.2 ± 13.9 – 103.2 ± 15.3 mmol/l). Five patients have been tapered off tacrolimus so far, nephrotic syndrome relapsed in 4 of them (80%). Relapse occurred at tacrolimus levels between 2.6 and 6.9 ng/ml. the study concluded that tacrolimus may be a promising alternative to cyclosporine both in steroid-resistant and steroid-dependent nephrotic syndrome.[27]

S. Gulati (2008) studied to see if Tacrolimus (TAC) was safe and effective for use in children with SRNS. 22 children with steroid-resistant nephrotic syndrome (SRNS) were included in the study group and were followed up. TAC was started at a dose of 0.10 mg/kg/day and escalated until a trough level of 5.0–10.0 g/l was reached. Prednisone was administered concurrently to these patients before being tapered off and ceased. The number of patients who had a complete remission (CR) or partial remission was the major outcome variable (PR). There were 20 boys and 2 girls, and the mean age at onset was 7.33 5.9 years. Of the 22 children, 11 exhibited focal segmental glomerulosclerosis, 9 had minimal change disease, and the remaining 2 had diffuse mesangial hypercellularity on histology. Children had to stop using TAC due to its negative effects. The other 19 children, who received sufficient therapy and were able to achieve their objectives saw CR in 16 (84%) of them, PR in 2 (10.5%), and 1 was nonresponsive. The mean TAC dose was 0.18 0.07 mg/kg, and the mean time to remission was 63.2 44 days. In comparison, the mean serum albumin levels were significantly higher (3.92 0.35 g/dl vs. 2.39 0.56 g/dl, p = 0.00005) and the mean urine spot protein/creatinine ratios were much lower (0.33 0.58 vs. 13.5 21.9 mg/mg, p = 0.002). At the conclusion of the study, the mean glomerular filtration rates were similar to those before TAC was started (97.9 21.2 vs. 96.4 18.4 ml/min/1.73m 2; p = 0.30). The average number of follow-up days was 290 +/- 126. The size of this study was the greatest to date on the security and effectiveness of TAC therapy in SRNS. Findings implied that TAC was a potent therapeutic option for SRNS, particularly for the subset of kids who do not respond to the standard treatments like cyclophosphamide and cyclosporine.[28]

Ren H. et al (2012) observed the clinical efficacy and safety of low dose tacrolimus (TAC) combined with tripterygium (TW) in treatment of steroid resistant nephrotic syndrome (SRNS). 20 SRNS patients in total, 11 from the TAC + TW group and 9 from the TW group, completed the experiment. In terms of age, gender, length of time since

disease onset, blood pressure, 24 hour UPQ, serum albumin, creatinine, cholesterol, triglyceride, Fasting blood glucose (FBG), categories of kidney pathology, timing of prednisone use, etc., there was no statistically significant difference between the two groups; Urine protein started to decrease after 1 month of treatment in both the TAC + TW and TW groups. By the 12th month of treatment, the TAC + TW group had 8 complete remissions (72.7%), 2 partial remissions (18.2%), and 1 case of no improvement (9.1%), compared to the TW groups' 2, 22, 22, and 4 (44.5%) complete remissions, partial remissions (18.2%), and 3 (33.3%) complete remissions, respectively. After starting treatment, the plasma protein of the TAC + TW group patients was significantly higher than that of pre-treatment stage. However, there was no appreciable increase in plasma protein in the TW Group. The incidence of adverse responses was not substantially different between the two groups, and there were no evident changes in the serum creatinine levels of the patients in either group.[29]

Supavekin S et al (2013) evaluated the efficacy of tacrolimus (Tac) in steroid resistant and steroid dependent nephrotic syndrome (NS) in children. The ratio of boys to girls was 2:1. At diagnosis, the average age was 6.0 years (1-14.4 years). Nine SR and nine SDNS were present. Four individuals had IgM nephropathy, two had minor change illnesses, and nine patients had focal segmental glomerulosclerosis (FSGS) (MCD). Three kids were not given kidney biopsies. At the beginning of Tac, prednisolone was given to all patients. An average of 3.5 years passed between the diagnosis and the start of TAC (0.2-14years). The average time of treatment for Tac was 1.3 years (0.3-6.2 years). The range for the average Tac trough blood level was 1.3–9.9, or 4.09 mcg/L. Tac was administered at an average dose of 0.09 mg/kg/day (0.03-0.2 mg/kg/day). Thirteen children (72.2%) responded completely (CR). Five children (27.80%) didn't respond to Tac. Nine children (69.2%) were able to discontinue taking prednisolone, while four (30.8%) were able to reduce their doses. The average number of days to reach CR was 24.6. (0.1-3 months). The average number of

follow-up years was 3.1. (0.2-6.4 years). An estimate of the glomerular filtration rate remained unchanged (eGFR). Four (44.4%) and five (55.6%) of the children in SRNS had CR, meaning that the FSGS did not respond to Tac. In SDNS, every patient responded to Tac, and four (44.4%) of the children relapsed while taking Tac and developed an upper respiratory infection (URI). [30]

Shah SS et al (2016) compared the efficacy of tacrolimus versus cyclosporine (Calcineurin Inhibitors) in the management of childhood steroid-resistant nephrotic syndrome (SRNS). Patients aged 1 to 12 years with mesangioproliferative glomerulonephritis, focal segmental glomerulosclerosis (FSGS), or minimal-change disease (MCD) were eligible. Patients were divided into two groups: one received tacrolimus at a dose of 0.1 - 0.2 mg/kg/day in two divided doses, while the other received cyclosporine at a dose of 150 to 200 mg/m2/day in two divided doses, as well as oral steroids at a dose of 30 mg/m2/day in divided doses, on alternate days with tapering dosage. Trough drug levels were measured and doses were adjusted accordingly. Patients' responses to treatment and the side effects of these two calcineurin inhibitors were monitored. A total of 84 patients, 58% males and 42% females, were included in the study. The age ranged from 1.25 to 12 years. The most common histopathological diagnosis was MPGN (69.04%), FSGS (21.4%), and MCD (9.52%). Complete response was seen in 80.95% and 97.6% patients treated with cyclosporine and tacrolimus, respectively. Partial response was in 19.05% patients treated with cyclosporine and 2.4% in patients with tacrolimus. The most common adverse effect with cyclosporine and tacrolimus was hypertrichosis in 80.95% and 2.38%, hypertension 16.66% and 11.9% respectively while gum hypertrophy with cyclosporine was seen in 26.19% patients. Tacrolimus was more efficacious than cyclosporine in achieving remission in childhood SRNS with insignificant adverse effects.[31]

Li S. et al (2017) conducted a network meta-analysis aimed at evaluating the efficacy and safety of available immunosuppressive agents in pediatric patients with SRNS. A meta-analysis of 18 RCTs showed that tacrolimus was more efficacious for achieving CR than intravenous cyclophosphamide, mycophenolate mofetil (MMF), oral cyclophosphamide, leflunomide, chlorambucil, azathioprine, plaebo/ nontreatment (P/NT) and more efficacious than i.v. cyclophosphamide, oral cyclophosphamide, and P/NT in terms of TR outcomes. Cyclosporin was associated with a greater CR rate than i.v. cyclophosphamide, MMF, oral cyclophosphamide, chlorambucil, azathioprine, or P/NT, and associated with a greater TR rate than i.v. cyclophosphamide, oral cyclophosphamide, or P/NT. MMF was found to be more efficacious than i.v. cyclophosphamide and oral cyclophosphamide in terms of TR. In contrast to cyclophosphamide given intravenously, MMF, oral cyclophosphamide, chlorambucil, azathioprine, or P/NT, cyclosporine was associated with a higher rate of CR and a higher rate of TR. In terms of TR, MMF was found to be more effective than intravenous and oral cyclophosphamide.[32]

Sarathlal MR et al (2018) Tacrolimus' effectiveness in treating steroid dependent and steroid resistant nephrotic syndrome was examined retrospectively (SDNS and SRNS). The study comprised 40 children who had SDNS and SRNS. For complete remission, partial remission, deterioration in renal function, and adverse medication effects, all patients were monitored. Complete remission was achieved in 14 children in SDNS group and 11 children in SRNS group. 3 children in SDNS group and 4 children in SRNS group did not achieve any remission despite treatment for 6 to 12 months. Adverse effects of the drugs included infections, tremors and hyperglycemia and were similar in both the groups. Mean duration of follow up of 24 months. It was concluded that tacrolimus was efficacious in inducing and maintaining remission in children with steroid dependent and steroid resistant nephrotic syndrome with minimal adverse effects.[33]

Butani L et al (2009) performed a single-center retrospective observational study to determine the tacrolimus remission rate in young patients with SNRS. Children receiving tacrolimus medication had their serial renal biopsies examined for tubulointerstitial fibrosis and immunostaining for transforming growth factor. 15 of the 16 children with SRNS experienced a full remission following a median of 120 days of treatment. Although the rest were on reducing doses, nine kids were able to quit using steroids. Relapses occurred in 47% of patients, the majority of which were amenable to steroids. Seven children underwent serial renal biopsies following a median treatment duration of 24 months; two of these children had increased tubulointerstitial fibrosis, and four of these children displayed increased tissue staining for transforming growth factor.[34]

TH Westhoff et al (2007) evaluated the tacrolimus in the treatment of idiopathic nephrotic syndrome. Despite the positive outcomes discussed in this analysis, tacrolimus is a nephrotoxic medication, and this needs to be underlined. Although the use of CsA in nephrotic syndrome was now widely accepted, treating a renal disease with a nephrotoxic medication is certainly not the best option. Furthermore, similar to CsA, a significant fraction of patients needing long-term medication for nephrotic syndrome experience relapses once tacrolimus was stopped. The main goal of all research on calcineurin inhibitor therapy in nephrotic syndrome to date was to reduce proteinuria. Development of GFR was only mentioned as a side effect, which, particularly in the case of FSGS, does not accurately reflect the nature of the underlying disease. Future studies should therefore concentrate on the use of novel, non-nephrotoxic immunosuppressants.[35]

What is Second-line drugs in nephrotic syndrome?

Fujimoto S (1991) 33 patients with adult-onset minimal change nephrotic syndrome were investigated for the rate of response to a corticosteroid and the frequency of relapse (MCNS). 28 of them

received oral prednisolone (PSL) at a dose of 1 mg/kg/d for 4 to 8 weeks, depending on their response, and then PSL at gradually declining levels for a year. Five patients with severe nephrotic disease got 40 mg/day of PSL orally for 4 to 8 weeks before receiving PSL at gradually lowered doses. They also received 1 g of methylprednisolone intravenously (IV) for 3 days. Within 4 weeks, proteinuria was gone in 16 individuals (48%) and in 25 patients (76%) within 8 weeks. Cyclophosphamide was required for the induction of remission in two cases. Age at presentation had no discernible relationship to how quickly patients responded to corticosteroid medication. Thirty-two (97%) of them entered remission, and 11 (34%) of them had relapse. According to the life-table technique, 63% of patients were still in remission during the follow-up period, 75% were at one year following the induction of remission, and 84% were after six months (mean, 47.1 +/- 29.1 months; range, 6 to 123 months). Relapse rates were higher in younger patients (less than 30 years of age) than in older patients (greater than or equal to 30 years) but were unrelated to the timing of remission induction, i.e., earlier (less than or equal to 4 weeks) or later (more than 4 weeks) (P less than 0.03). 31 patients (94%) were in complete remission and had normal renal function at the most recent check-up.[36]

Neuhaus et al (1994) performed study and used alternative treatment in children with SSNS in the nephrology unit at Great Ormond Street Hospital for Children, London. The alternative therapy used included levamisole, cyclophosphamide, cyclosporine, chlorambucil, azathioprine and vincristine. The study found that half of the 429 children studied were given at least one course of alternative drugs, 25% received two courses and 5% were administered four or more courses. Cyclophosphamide was the most frequently used drug and out of the children who received cyclophosphamide, 50% were able to achieve either prolonged remission or were maintained at a lower dose of alternate day steroids. The functioning of gonads in both the sexes

remained unaffected up to a cumulative dose of 500 mg/kg of cyclophosphamide.[37]

Alsaran K. (2017) performed a retrospective study over a period of 3 years on the use of 4 second line drugs in FR/SD nephrotic syndrome in children treated at our center. These drugs were Levamisole, Mycophenolate Mofetil (MMF), Cyclophosphamide, and Cyclosporine and studied the relapse rate per year, cumulative dose of steroids, success, failure, and side effects of these drugs. Statistical analyses were done with the help of a statistician using the T-test and the "N-1"Chi–Square test. We reviewed the charts of 60 children. All had FR/SD nephrotic syndrome and received a 3 month protocol of prednisolone. 20 received Levamisole (33%), 12 received Cyclophosphamide (20%), 20 received MMF (25%), and 13 received Cyclosporine (22%). All the four drugs significantly reduced the relapse rate and the cumulative dose of steroids ($P < .0001$). Treatment success was best with Cyclosporine (69.2%), and treatment failure was the least with Cyclosporine (7.6%). However, treatment success and failure with Cyclosporine when compared to other three drugs was not statistically significant. No dangerous side effects were seen with any of the 4 drugs in the observation period. All the second line drugs in our study were equally effective. They recommend that the initial treatment of FR/SD nephrotic syndrome should be chosen with the least toxic yet equally efficacious drug Levamisole.[38]

Moorani KN (2019) performed a retrospective cohort study of 176 children with DNS, managed over 12 years at The Kidney Center-Postgraduate Training Institute, Karachi- Pakistan from 2005 to 2017. Initial episode was treated with daily oral prednisolone (OP) for 4–8 weeks followed by alternate day OP for 12–24 weeks. Subsequently low dose OP, levamisole (Leva)and cyclophosphamide was used for frequent relapsing (FR)/ steroid dependent (SD). All with initial steroid resistance and non- responders to leva and or cyclophosphamide were biopsied and treated with CNIs and MMF. Data was analyzed using

descriptive statistics. Majority had steroid sensitive MCD. Levamisole and cyclophosphamide were effective in maintaining remission in FR/ SD. FSGS was responsible for resistance to steroid and alternative ISAs. Cyclosporin was effective in inducing remission in SRNS. Mortality was less than 3%.[39]

Histological pattern in nephrotic syndrome

Ibrahim Seif E et al (2013) determined the histological patterns of ISRNS in Egyptian children and the histological details of the commonest types which might be the reason for the steroid resistance. Performed a single centre study and FSGS, MCG, and IgA nephropathy were the major histological patterns of childhood idiopathic steroid resistant nephrotic syndrome in Egypt. Renal biopsy with electron microscopy examination should be done at the first time of presentation to choose the correct treatment protocol. Nephrotic syndrome with a fair steroid response might turn resistant after certain duration of follow up due to change of the renal histological pattern.[40]

Rahbar, M. (2016) reviewed Review of Idiopathic Steroid Resistant Nephrotic Syndrome and Outcome in Children in North-West of Iran. In children in the northwest of Iran, this study outlined the full range of clinicohistopathology characteristics that underlie SRNS. This study also demonstrated that the histopathological patterns revealed by an appropriate kidney biopsy can be used to correlate the response to cyclosporine. This study demonstrated a relationship between the cyclosporine reaction and the underlying pathological lesion. Therefore, before beginning treatment with potentially nephrotoxic drugs, a kidney biopsy should be the initial step.[41]

Newer treatment of nephrotic syndrome in pediatric patients

Kim J et al (2014) at a single tertiary treatment center, a retrospective chart analysis of paediatric patients with idiopathic nephrotic syndrome was carried out (2007-2012). Drug reactions were divided into three categories: full response, moderate response, and no response. With

good results and better side effect profiles, newer drugs including MMF, tacrolimus, and rituximab can replace older ones. For tacrolimus, the response rate was 96% (22/23) for SSNS and 77% (17/22) for SRNS. Eighty-three percent (5/6) of SSNS subjects treated with rituximab went into complete remission; 60% relapsed after B-cell repletion. Eight refractory subjects were treated with combined MMF/tacrolimus/ corticosteroid therapy with a 75% response rate. The study concluded that older medications can be replaced with newer ones such as MMF, tacrolimus, and rituximab with good outcomes and better side effect profiles. The treatment of refractory cases with combination therapy is promising. [42]

Afsana et al (2015) analyzed the relationship between inter-dose area under the concentration curve (AUC0-12 h) and trough concentration and the therapeutic effectiveness of tacrolimus in children with SRNS. In SRNS, tacrolimus produced a favourable clinical response. Children with SRNS had target C0 and AUC012 h levels that were higher than those in remission, but they were lower than necessary for transplant recipients.[43]

Pokrajac D (2018) evaluated steroid resistant nephrotic syndrome patients. The research was performed in 50 children and drugs used were drugs used in SRNS were Cyclosporine (CsA), Cyclophosphamide (CYC), Mycophenolate mofetil (MMF) and Rituximab (RTX) and concluded that with current treatments, some children will eventually achieve a sustained remission with one of the proposed drugs in the second or third line. Patients with refractory NS will eventually develop ESRD. The rapid advancement of molecular genetics will contribute significantly to the pathogenesis and treatment of this disease.[44]

Kemper MJ et al (2018) confirmed that effectiveness of calcineurin inhibitors (CNIs) and mycophenolic acid in preventing SSNS relapses. Rituximab also played an important role, but many questions about initial dosing, course repetitions, and long-term side effects remain

unanswered. Chronic kidney disease can result from SRNS, especially if it was unresponsive to treatment. Treatment with CNIs, in particular, has improved the prognosis, and recent data suggested that treatment can even be stopped in many patients who are in full remission.[45]

Tullus K et al (2018) concluded that following daily treatment with corticosteroids, more than 85% of children and adolescents (often between 1 and 12 years old) with idiopathic nephrotic syndrome exhibited complete remission of proteinuria. Patients with steroid resistant nephrotic syndrome do not exhibit remission despite receiving daily prednisolone for 4 weeks of treatment (SRNS).The majority of patients' renal histology revealed the presence of minimal change disease, localised segmental glomerulosclerosis, and (occasionally) mesangio proliferative glomerulonephritis. One of the important podocyte genes had mutations in onethird of SRNS patients. The remaining SRNS instances were most likely brought on by an unidentified circulating component. For the treatment of hypertension and to lessen any remaining proteinuria, further renin-angiotensin axis inhibitor therapy was advised. End-stage renal failure was a possibility in SRNS patients who do not react to treatment with calcineurin inhibitors or other immunosuppressive medications and who exhibited deteriorated kidney function. Recurrent focal segmental glomerulosclerosis in the allograft was present in around one third of recipients of renal transplants, and this condition frequently responded to a combination of plasma exchange, rituximab, and enhanced immunosuppression.[46]

Trautmann A et al (2018), investigated the characteristics and phenotypes of immune mediated and genetic forms of childhood SRNS, and determined the relationships between genotype and phenotype, assessed clinical management and longterm outcomes, and looked for new genetic entities and diagnostic and prognostic biomarkers in SRNS. PodoNet Registry has collected detailed clinical and genetic information in a large SRNS cohort and continued to

generate fundamental insights regarding demographic and etiological disease aspects, genotype-phenotype associations, the efficacy of therapeutic strategies, and long-term patient and renal outcomes including post-transplant disease recurrence.[47]

Comparison between tacrolimus and cyclosporine in treatment of nephrotic syndrome

Y. Ravanshad et al (2019) the systematic review included four randomised controlled studies that were eligible. No discernible changes were seen between tacrolimus and cyclosporine in terms of partial and total remission. When compared to cyclosporine, tacrolimus's lack of a therapeutic response was, however, markedly reduced (RR=0.289; P=0.02). Infection rates, hypertension, ALT/AST elevation, and gastrointestinal symptoms were not significantly different between the drugs, but tacrolimus had significantly lower rates of nephrotoxicity and hypertrichosis (RR=0.395 and RR=0.018, respectively; P=0.004) and hypertrichosis (RR=0.018 and P0.001) than the other drugs. Tacrolimus is preferable to cyclosporine in the treatment of patients with steroid resistant nephrotic syndrome in terms of no response to therapy, nephrotoxicity, and hypertrichosis.[48]

Zaorska K et al (2021) predicted steroid resistance and steroid dependence in nephrotic syndrome children. The strongest predictors were ABCB1 rs1922240, rs1045642, and rs2235048, CD73 rs9444348 and rs4431401, serum creatinine, and the unmethylated SOCS3 promoter region, which achieved 92% (AUC = 0.778) SR prediction for binomial calculations and 63% for multinomial calculations. Following that, we achieved 80% (AUC = 0.720) in binomial prediction of SD and 63% in multinomial prediction, with the strongest predictors being ABCB1 rs1045642 and rs2235048. CD73 AG was associated with SR, while ABCB1 AGT was associated with SR, SD, and a membranoproliferative pattern of kidney injury regardless of steroid response.[49]

Choudhary et al (2009) The study aimed to determine whether tacrolimus is more effective and safer than cyclosporine in inducing remission in patients with steroid-resistant nephrotic syndrome. The study included 41 patients who were randomly assigned to treatment with either tacrolimus or cyclosporine for a year, along with alternate-day prednisolone and enalapril. The primary outcome was the proportion of patients achieving complete or partial remission at 6 and 12 months, while the secondary outcomes included time to remission, relapse rates, and side effects. The study found that both tacrolimus and cyclosporine were equally effective in inducing remission at 6 and 12 months. However, patients treated with tacrolimus had a lower risk of relapse and experienced greater decreases in blood cholesterol levels. Cosmetic side effects were more frequent in patients treated with cyclosporine. The study's limitations include a small sample size, short duration of follow-up, and a single-center study design. In conclusion, the study suggests that tacrolimus and cyclosporine are equally effective in inducing remission in patients with steroid-resistant nephrotic syndrome, but tacrolimus may have some advantages over cyclosporine in terms of relapse rates and lipid profile. [50]

Comparison of steroid in relation to Tacrolimus in patients with nephrotic syndrome

Chin HJ et al (2021) concluded that in both the intent-to-treat (11.6%) and per protocol (17.0%) analyses, complete remission occurred in 53 of 67 patients (79.1%) receiving tacrolimus and low-dose steroid and 53 of 69 patients (76.8%) receiving high-dose steroid; this difference demonstrated noninferiority, with an upper confidence limit below the predefined threshold (20%). The time until remission did not differ significantly between groups. Maintenance tacrolimus (3 to 8 ng/ml) plus tapered steroid resulted in significantly fewer relapses than tapered steroid alone (5.7% versus 22.6%, respectively; P=0.01). There were no clinically significant differences in safety.[51]

Vasudevan A et al (2021) recommended that paediatric nephrologist should manage the treatment of patients with SRNS. Updated guidelines for identifying steroid resistance were provided in fourteen statements, which further stress the necessity of determining proteinuria and baseline renal function as well as kidney biopsy and genetic testing. Proteinuria is the main factor related with longterm renal survival, and calcineurin inhibitors were advised as being the most efficient in inducing remission of this condition. Congenital nephrotic syndrome, allograft recurrence, and monitoring and supportive care, including the transition of care, were addressed. The goal of this updated practise recommendation was to enhance management, patient outcomes, and give guidance for future research.[52]

Sehrawat KS et al. (2021) a retrospective analysis of follow-up patients sent to the Drug Assay Lab was conducted. From January 2021 to April 2021, tacrolimus was therapeutically monitored for the SRNS patients. 55 children with steroid-resistant nephrotic syndrome had their clinical profiles evaluated. Tacrolimus test results and these patients' hospital patient cards were used to analyse the data. Patients demonstrated partial remission in 30.90% of cases and complete remission in 61.81% of cases. Children with tacrolimus therapy showed better treatment outcomes.[53]

Comparison between efficacy of Rituximab and Tacrolimus

Mathew G et al (2022) performed a open label pilot randomized controlled trial on efficacy of Rituximab versus tacrolimus in difficult to treat steroid sensitive nephritic syndrome. In patients with difficult-to-treat steroid-sensitive nephrotic syndrome, treatment with rituximab was not demonstrated to be non-inferior to 12-months of tacrolimus. With rituximab, frequent relapses were more typical. Both medications, however helpful, need to be closely watched for side effects.[54]

Basu B et al (2018) performed randomized clinical trial that included 120 children with corticosteroid-dependent nephrotic syndrome, a single course of rituximab therapy was associated with a significantly higher 12-month relapse-free survival rate than daily tacrolimus therapy (90.0% vs 63.3%) during 12 months of follow-up. The mean cumulative corticosteroid dose during the 12-month study period was lower with rituximab compared with tacrolimus (25.8 vs 86.3 mg/kg). In children with corticosteroid-dependent nephrotic syndrome, rituximab is more effective than tacrolimus in maintaining disease remission and may be considered as first-line corticosteroid-sparing therapy.[50]

Ambarsari C et al (2022) concluded that children with refractory SRNS can be completely cured with rituximab and a combination of CNIs and MPA, while children with FSGS with FRNS and SRNS can have their remission last for years. This course of treatment offered the benefit of removing the need for ongoing, highdose steroid therapy, allowing one patient to regain normal growth and recover from various side effects of steroid use.[56]

Sinha et al (2011) conducted a study which retrospectively reviewed the records of patients with difficult-to-treat steroid-dependent nephrotic syndrome (SDNS) who were treated with either rituximab or tacrolimus and followed for 12 months. The study found that therapy resulted in a decline in relapse rate in both groups, with no significant difference in the number of relapses or relapse-free survival at 6, 12, and 18 months. The cumulative prednisolone dose decreased significantly in both groups, with a reduced body mass index. The study suggests that treatment with two to three doses of rituximab was as effective as 12 months of therapy with tacrolimus in terms of steroid sparing and reduction in the relapse rate in patients with difficult-to-treat SDNS. However, the study is limited by its small sample size and retrospective design.[57]

Comparison between efficacy of Tacrolimus and Mycophenolate mofetil

Wang J et al (2016) conducted a single-center prospective study to compare the efficacy of MMF or TAC in reducing relapses and maintaining remission in children with FRNS or SDNS. Of the 72 recruited patients, either MMF (20~30 mg/kg/d, n = 34) or TAC (0.05~0.15 mg/kg/d, n = 38) was administered for 12 months. They reported the mean 6-month relapse rates decreased from 2.56 episodesbefore therapy to 0.76 episodes in the first 6 months after therapy ($c2 = 44.362$, $p < 0.001$) and 0.67 in the next 6 months ($c2 = 37.817$, $p < 0.001$) in the MMF group. In the TAC group, the mean 6-month relapse rates decreased from 2.39 episodes before therapy to 0.41 episodes in the first 6 months after therapy ($c2 = 62.242$, $p < 0.001$) and 0.42 in next 6 months ($c2 = 67.482$, $p < 0.001$). No significant difference in the relapse rate was found between the groups (before therapy, $c2 = 0.902$, $p = 0.637$; first 6 months, $c2 = 5.358$, $p = 0.147$; second 6 months, $c2 = 4.089$, $p = 0.252$). And there was also no significant difference in cumulative sustained remission and the incidence of adverse events between two groups. In combination with low-dose steroids, MMF or TAC presented similar efficacy in maintaining remission in children with FRNS/SDNS. [58]

STAMP (2021) study mainly compared the efficacy and safety of tacrolimus and mycophenolate mofetil in the treatment of children with frequently relapsing or steroids-dependent nephrotic syndrome, in order to provide a more effective and safer treatment for children with nephrotic syndrome as well as the therapeutic medication options. Although the treatment of steroids with immunosuppressive agents is a new choice for the treatment of such patients, traditional immunosuppressive agents such as cyclophosphamide and cyclosporine A will bring some serious irreversible side effects, while immunosuppressive agents tacrolimus has the dual effects of immunosuppression and podocyte protection, and is more widely used

in the department of nephrology, what's more, the other immunosuppressive agents mycophenolate mofetil has advantage of no kidney toxic, less adverse reactions and higher safety, which gradually being valued by nephrologists in recent years.[59]

Sinha A et al (2017) performed open-label, one-to-one randomised, controlled trial on kids (aged one to 18) with recently identified steroid-resistant nephrotic syndrome at a referral centre in India looked at the impact of switching from tacrolimus medication to MMF on disease course. Following six months of tacrolimus therapy, patients in complete or partial remission were randomly assigned to receive MMF or tacrolimus combined with tapering prednisolone on alternate days for a 12-month period in 29 patients and tacrolimus in 31 patients. Intention-to-treat analyses revealed that the tacrolimus group had a significantly higher percentage (90.3%) of patients with a good outcome (persistent remission, uncommon relapses) after one year than the MMF group (44.8%) did. Those receiving MMF treatment relapsed more frequently than those receiving tacrolimus, by a substantial margin (mean difference: 1.05 relapses per person-year). While there was no difference in the percentage of patients who experienced prolonged remission, patients receiving MMF compared to tacrolimus had a considerably higher risk of developing steroid resistance again (mean difference: 20.7%). Patients using MMF had a significantly (71%) reduced chance of a positive outcome and a significantly higher risk of therapy failure when compared to tacrolimus (frequent relapses, steroid resistance). Following six months of tacrolimus therapy for children with steroid-resistant nephrotic syndrome, switching to MMF carries a substantial risk of repeated relapses or recurrence of resistance.[60]

Association between genetic and clinical phenotypes

Jiao J et al (2022) Understood the association between the genetic and clinical phenotypes in children with nephrotic syndrome of different etiologies is critical for early clinical guidance. With a complete

remission rate of 49.7% in patients with idiopathic SRNS, tacrolimus (TAC) demonstrated the highest response rate. Only 31.4% of individuals with monogenic disease were able to obtain a partial remission on TAC in idiopathic SRNS patients who had the same pattern of multidrug resistance. Idiopathic SRNS patients with monogenic disease advanced to endstage renal disease in 21.4% of cases over an average of 4.1 years of followup (ESRD). Collectively, this research shows that genetic testing is required for individuals with suspected idiopathic and steroidresistant SRNS, especially those who have primary and multidrug resistance.[61]

McKay AM et al (2023) concluded that few reported trials have focused at long-term remission; most have concentrated on short-term outcomes including time to first relapse and relapse rates up to 1-2 years of follow-up. The heterogeneity of pathogenic mechanisms, as well as genetic and environmental variables, resulted in different responses to therapies, yet trial designs frequently do not take inter-individual variability into account. The integration of biomarkers, novel trial designs, and standardised outcomes were suggested as strategies to increase the amount and quality of trials in steroid sensitive nephrotic syndrome, particularly for long-term remission.[62]

MATERIAL AND METHODS

It was a hospital based observational study of patients with steroid dependent and steroid resistant nephrotic syndrome who were treated with tacrolimus with a follow-up of at least one year in Paediatric Nephrology clinic in the Department of Paediatrics of Dayanand Medical College and Hospital, Ludhiana, Punjab.

Study design:

It was a hospital based observational study, including 43 patients of steroid dependent and steroid resistant nephrotic syndrome. We followed up patients who were already enrolled as well as new patient registered in Paediatric Nephrology clinic in the Department of Paediatrics of Dayanand Medical College and Hospital, Ludhiana Punjab.

Source of data:

Patients of steroid dependent or steroid resistant nephrotic syndrome between 3 months to 18 years of age who received tacrolimus earlier and/or were receiving tacrolimus with a follow-up of at least one year in Paediatric Nephrology clinic in Department of paediatrics, DMCH, Ludhiana.

Inclusion criteria:

All patients of steroid dependent or steroid resistant of nephrotic syndrome between 3 months to 18 years of age, who had received tacrolimus with a follow-up of at least one year in Paediatric Nephrology clinic in the Department of paediatrics DMCH.

Exclusion criteria:

1. Patients of congenital nephrotic syndrome (age of onset <3 three months)

2. Patients with nephrotic syndrome secondary to membranoproliferative glomerulonephritis or membranous nephropathy
3. Serum creatinine level greater than 1.5 mg/dL, estimated glomerular filtration rate[17]less than 60 mL/min/1.73 m^2.
4. History of diabetes mellitus or liver disease
5. If attendants refused to give consent for participation in the study.
6. Follow up less than 1 year.

Primary outcome:

The primary end point was the proportion of patients achieving complete or partial remission at the end of 6 months of therapy.

Secondary outcomes:

To study time to achieve remission, proportion of participants in remission at 12 months, frequency of relapses, and side effects of tacrolimus.

Definition as per KDIGO 2020[63]

- SSNS: complete remission after 4 weeks of prednisone or prednisolone at standard dose
- Infrequent relapsing NS: <2 relapses per 6 months or <4 relapses per 12 months
- Frequent relapsing NS: ≥2 relapses per 6 months or >4 relapses per 12 months
- Steroid-dependent NS: relapses during therapy with prednisone or prednisolone (either at full dose or during tapering) or within 15 days of prednisone or prednisolone discontinuation
- SRNS: lack of complete remission at 4 weeks of therapy with daily prednisone or prednisolone at standard dose
- Late responder: complete remission at 6 weeks.

- Calcineurin inhibitor-responsive SRNS: partial remission after 6 months of treatment and/or complete remission after 12 months of treatment with a calcineurin inhibitor at adequate doses and/or levels
- Calcineurin inhibitor-resistant SRNS: absence of partial remission after 6 months of treatment with a calcineurin inhibitor at adequate doses and/or levels
- Multi-drug resistant SRNS: absence of complete remission after 12 months of treatment with 2 mechanistically distinct steroid-sparing agents at standard doses (see below)
- Secondary SRNS: a SSNS patient at disease onset who at a subsequent relapse fails to achieve remission after 4 weeks of therapy with daily prednisone or prednisolone at standard dose

Status of patients will be defined according to the following categories complete remission, Partial Resistance, No Response and Treatment Failure

Complete remission

Urine protein nil-trace by dipstick for 3 consecutive days, Up/Uc < 0.2, or 24-h protein < 100 mg/m2/day and serum albumin level of 2.5 g/dL or greater;

Partial remission

Urine protein 1+/2+ (dipstick), Up/Uc between 0.2-2, or 24-h urine protein 100-1000 mg/m2/day; serum albumin level of 2.5 g/dL or greater; ; and absence of edema

No response

Urine protein 3+/4+ (dipstick), Up/Uc ≥ 2, or 24-h urine protein > 1000 mg/m2/day; albumin < 2.5 g/dL or edemaSteroid resistance- Absence of remission despite therapy with daily prednisolone at a dose of 2 mg/kg per day for 4 weeks.

Treatment failure

Defined in patients having 3 or more relapses in 12 months while on treatment, Recurrence of SR (no response after relapse, after 4 weeks full dose steroids), persistent nephrotoxicity, or death.

The detailed demographic data like age, gender, education status of all included patients with details of their registration in the Pediatric Nephrology clinic was documented.

Classification of Response-

Responder, Patient who are in complete remission/ partial remission at 6 month of treatment.

Non Responder, Patient showing no remission to treatment at 6 month.

Data regarding age at onset of nephrotic syndrome, presence of hypertension, haematuria at the onset of disease, drugs (steroids or steroid-sparing agents) received before administering Tacrolimus were entered in proforma.

The status of patients before starting tacrolimus (steroid-dependent or steroid resistant NS) was established.

In SDNS and SRNS patients, the number of relapses and the dependent dose of steroids prior to tacrolimus were recorded.

Patients were screened for various side effects associated with a prolonged course of steroids usually seen in steroid-dependent and steroid resistant NS patients -

- Cataract
- Hypertension
- Gastritis
- Pancreatitis
- Fracture
- Short Stature
- Obesity/Overweight

Subjects included in the study were treated with tacrolimus at a dose of 0.1 to 0.2 mg/kg/day for 1 year; co-treatment with alternate day prednisolone.
Age of starting and duration of illness before starting tacrolimus was recorded.
If patients encountered any side effects during the course of tacrolimus, it was documented.

Adverse effects monitored with tacrolimus were Hypertension, Diarrhea, UTI, Reversible Nephropathy, Skin infections, Hyperkalemia, Seizure, Increase Blood Sugar, Increase OT/ PT, Hypertrichosis, Gingival Hyperplasia, Acne or any major infection requiring hospital admission.

Any interruptions during the course of tacrolimus were documented

If the patient suffered from any major infection or required hospitalization, the drug was temporarily stopped and restarted later.

Patients were followed up for at least 1 year while on tacrolimus course and their status was reviewed.

Tacrolimus levels were done every alternate month to maintain target trough level between 4-7 ng/ml.

Parameters like time to first relapse, the duration for which steroids were stopped, dependent dose and number of relapses post one year treatment with tacrolimus were documented.

Depending upon the clinical and laboratory parameters, patients were categorized as-
Complete remission: Urine protein nil-trace by dipstick for 3 consecutive days, Up/Uc < 0.2, or 24-h protein < 100 mg/m2/day and serum albumin level of 2.5 g/dL or greater;

Partial remission: Urine protein 1+/2+ (dipstick), Up/Uc between 0.2-2, or 24-h urine protein 100-1000 mg/m2/day; serum albumin level of 2.5 g/dL or greater; and absence of edema

No remission: Urine protein 3+/4+ (dipstick), Up/Uc ≥ 2, or 24-h urine protein > 1000 mg/m2/day; albumin < 2.5 g/dL or edema.

Based upon their status at 6 and 12 month, patients were classified as either –

Responder, Patient who are in Complete remission/ Partial remission at 6 month of treatment.

Non Responder, Patient showing no response to treatment.

Duration of tacrolimus received was noted along with the requirement of steroid at the end of 1 year. If the patient was off steroid, time taken to get off steroid and duration off steroid was entered. If patient was still on steroid, steroid dependant dose was entered. Parameters like first relapse after starting tacrolimus, number of relapses in 12 month period after tacrolimus were entered in the performa. If tacrolimus was stopped, renal functions were evaluated along with reason for stopping and if patient was started on subsequent therapy with rituximab.

Patients who were labelled as treatment failure, cause was evaluated and entered.

Results of renal function tests and urine routine analysis done for all patients was noted.

Histopathological results were recorded in those who underwent renal biopsy.

Height, weight, BMI and blood pressure of all patients were recorded at each visit and underwent an eye examination annually to rule out the development of cataract. Z- scores for height, weight and BMI were calculated in all patients. Based upon the values of Z scores for the

height, patients were labeled as having short stature or normal height. Patients with a Z- score of height less than 2 Standard Deviation was defined to have short stature. On the basis of BMI, patients were diagnosed to be overweight, obese or underweight.

If patients were receiving any drugs (steroids or steroid-sparing agents) at the time of enrolment in the study, those were entered in proforma.

STATISTICAL ANALYSIS

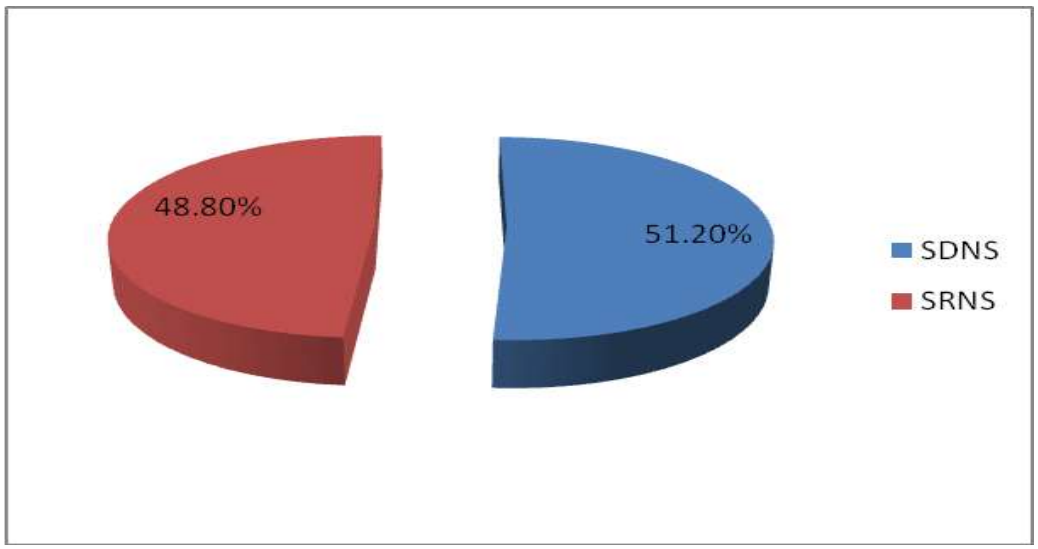
Data were described in terms of range; mean ±standard deviation (± SD), frequencies (number of cases) and relative frequencies (percentages) as appropriate. To determine whether the data were normally distributed, a Kolmogorov-Smirnov test was used. Comparison of quantitative variables between the study groups was done using Student t-test and Mann Whitney *U* test for independent samples for parametric and non-parametric data respectively. For comparing categorical data, Chi square ($\chi 2$) test was performed and fisher exact test was used when the expected frequency is less than 5. A probability value (*p* value) less than 0.05 was considered statistically significant. All statistical calculations were done using (Statistical Package for the Social Science) SPSS 21version (SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows.

OBSERVATIONS & RESULTS

TABLE NO.1: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON NUMBER

	No. of cases	%age
SDNS	22	51.2%
SRNS	21	48.8%

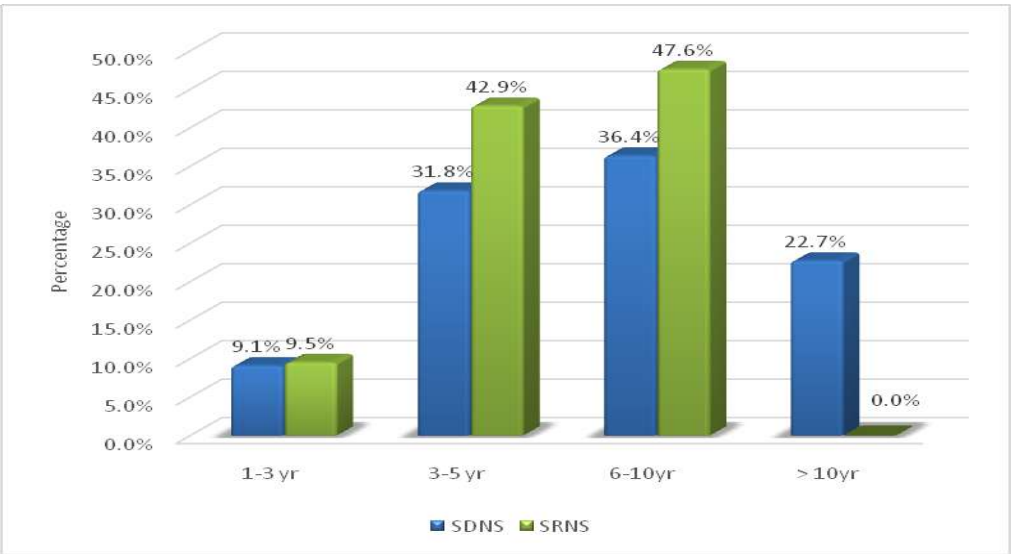
A total of 43 patients were enrolled in the study who met the inclusion criteria. 22 & 21 patients were in SDNS and SRNS group.



FIGUREURE NO.1: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON NUMBER

TABLE NO.2 (A): DISTRIBUTION OF STUDY PARTICIPANTS BASED ON AGE

	SDNS		SRNS		Total		Z	p-value
	Median	IQR	Median	IQR	Median	IQR		
Age (YEARS) (at enrollment)	6.8	4-10.25	5.0	3.3-6	3.8	2-5	-1.801	0.072
Age Of Onset of NS	3.5	1.575-5	4.0	2.7-4.75	5.5	4-8	-0.817	0.414



FIGUREURE NO.2 (A) DISTRIBUTION OF STUDY PARTICIPANTS BASED ON AGE

TABLE NO.2 (B) DISTRIBUTION OF STUDY PARTICIPANTS BASED ON AGE

		SDNS		SRNS		Total		Chi-square value	p-value
		cases	%	cases	%	cases	%age		
Age group	1-3 yr	2	9.1%	2	9.5%	4	9.3%	5.452	0.142
	3-5 yr	7	31.8%	9	42.9%	16	37.2%		
	6-10yr	8	36.4%	10	47.6%	18	41.9%		
	> 10yr	5	22.7%	0	0.0%	5	11.6%		
Total		22	100.0%	21	100.0%	43	100.0%		

The median age of study participants was 3.8 IQR (2-5). Median age in SDNS (Steroid-Dependent Nephrotic Syndrome) and SRNS (Steroid-Resistant Nephrotic Syndrome) was observed to be 6.8 IQR (4-10.25) and 5 IQR (3.3- 6) years respectively.

The median age of onset of NS (Nephrotic Syndrome) of study participants was 5.5 IQR (4-8). The median age in SDNS (Steroid-Dependent Nephrotic Syndrome) and SRNS (Steroid-Resistant Nephrotic Syndrome) was observed to be 3.5 IQR (1.575-5) and 4 IQR (2.7-4.75) years respectively. The distribution of study participants based on age between two groups of patients was not found to be statistically significant ($p>0.05$).

The maximum number of patients in the SDNS and SRNS groups were between 6-10 years (36.4% and 47.6% respectively) followed by age between 3-5 years (31.8% and 42.9).

Both groups had 2 patients in between 1-3 years.

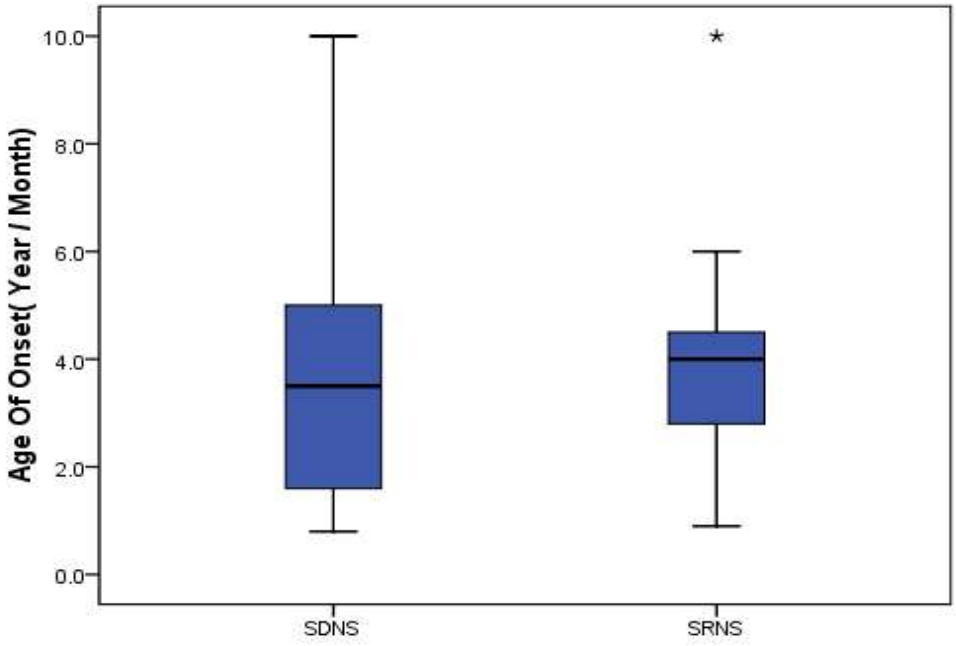


FIGURE NO.2B: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON AGE

TABLE NO.3: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON GENDER

		SDNS		**SRNS**		Total		Chi-square value	p-value
		No. of cases	%age	No. of cases	%age	No. of cases	%age		
Sex	F	4	18.2%	5	23.8%	9	20.9%	0.206	0.650
	M	18	81.8%	16	76.2%	34	79.1%		
Total		22	100.0%	21	100.0%	43	100.0%		

The study population showed male predominance. There were 81.8% males and 18.2% females among patients with SDNS and 76.2% males and 23.8% females among patients with SRNS. The distribution of study participants based on gender between two groups of patients was not found to be statistically significant (p>0.05).

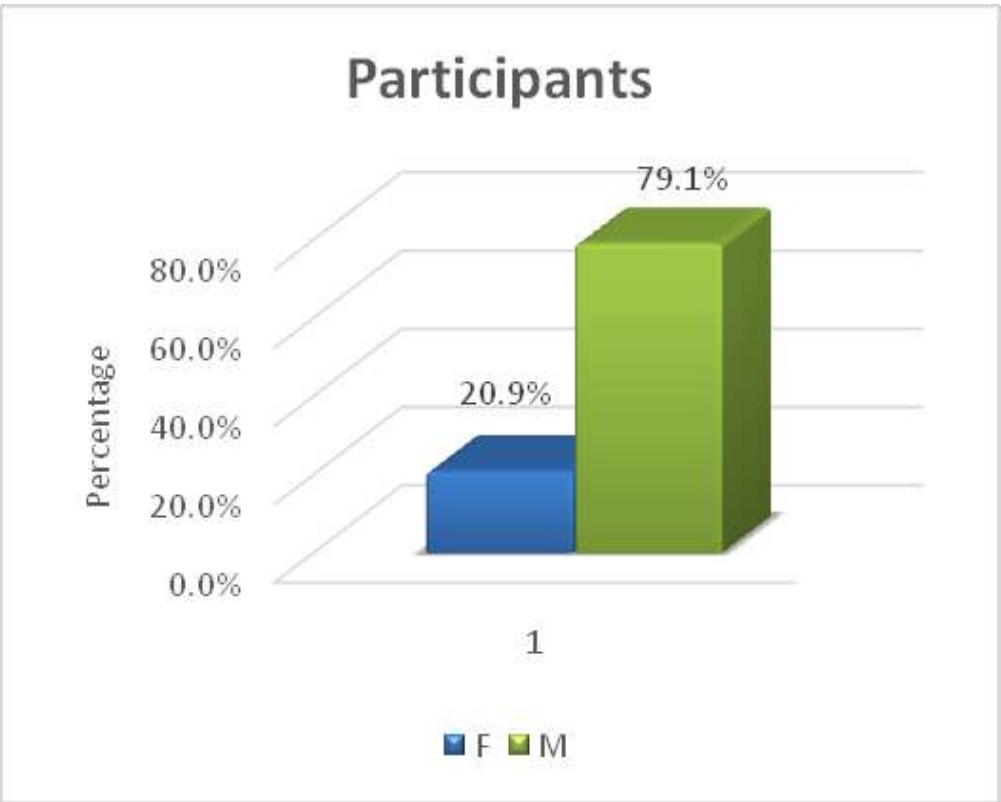


FIGURE NO.3A : DISTRIBUTION OF TOTAL STUDY PARTICIPANTS BASED ON GENDER

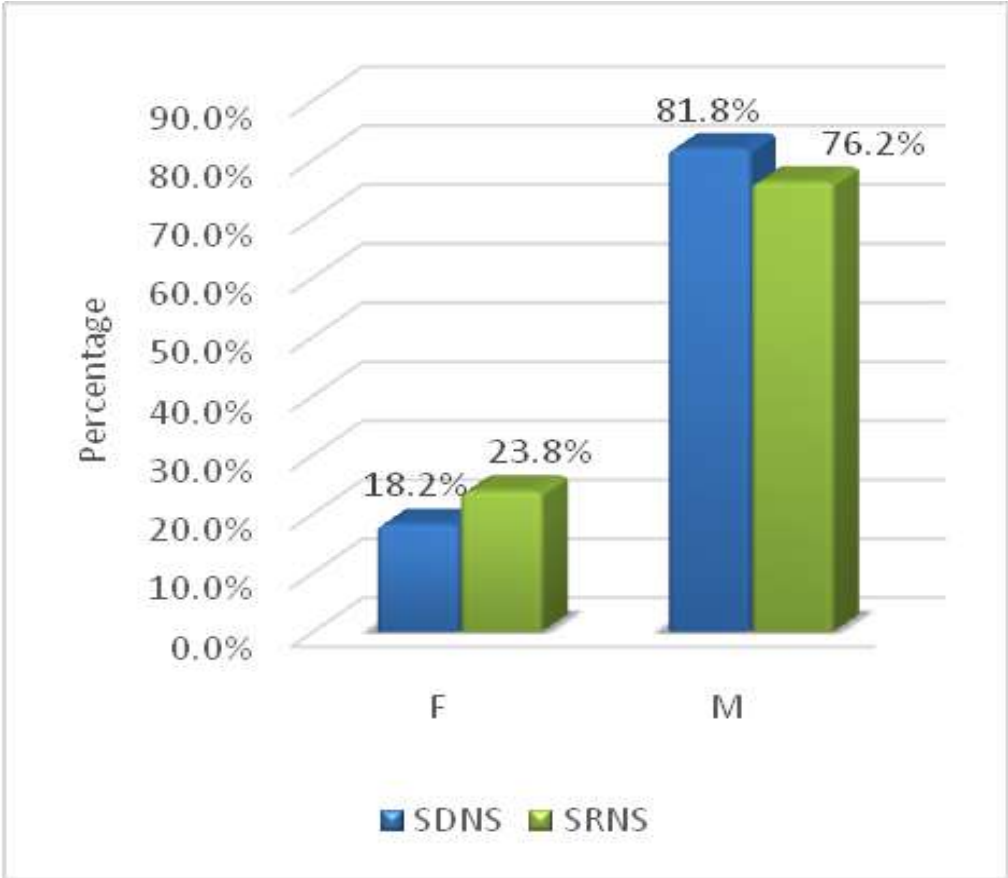


FIGURE NO. 3B: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON GENDER

TABLE NO.4: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON RESIDENCE

		SDNS		SRNS		Total		Chi-square value	p-value
		No. of cases	%age	No. of cases	%age	No. of cases	%age		
Urban/Rural	R	6	27.3%	4	19.0%	10	23.3%	0.407	0.523
	U	16	72.7%	17	81.0%	33	76.7%		
Total		22	100.0%	21	100.0%	43	100.0%		

It was observed that majority of study participants were from urban areas. Among patients with SDNS, 72.7% resided in urban areas and 27.3% resided in rural areas. Among patients with SRNS, 81% resided in urban areas and 19% resided in rural areas. The distribution of study participants based on residence between two groups of patients was not found to be statistically significant (p>0.05).

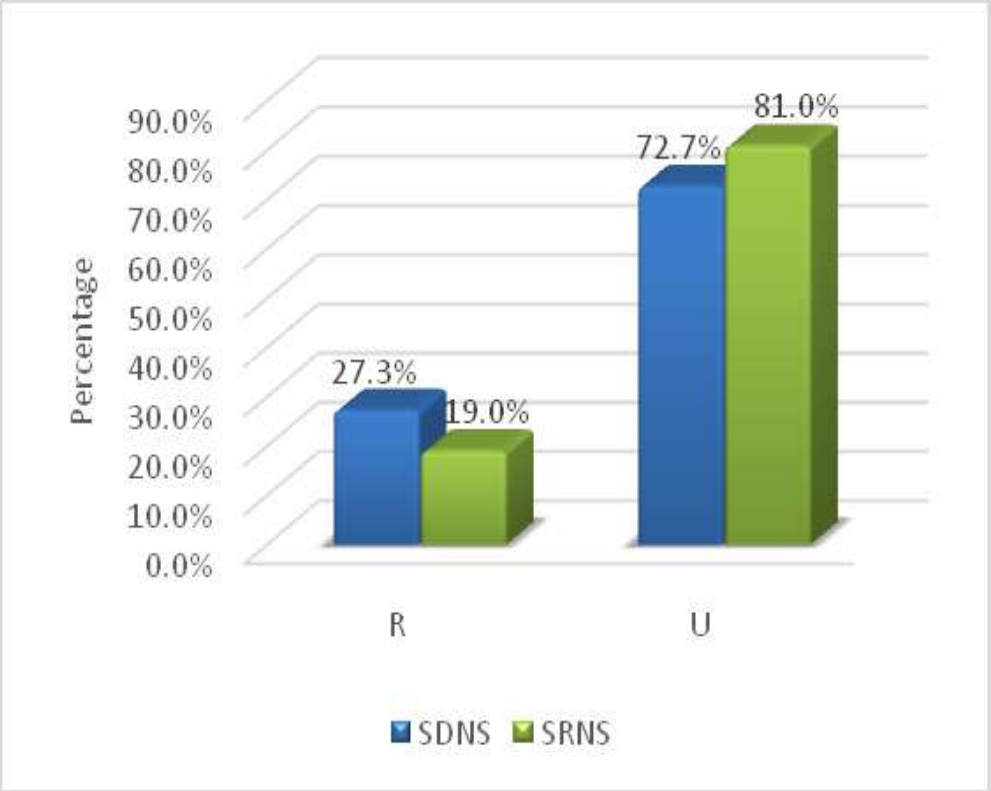


FIGURE NO.4: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON RESIDENCE

TABLE NO.5: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON HYPERTENSION AT ONSET OF NEPHROTIC SYNDROME

		SDNS		SRNS		Total		Chi-square value	p-value
		No. of cases	%age	No. of cases	%age	No. of cases	%age		
Hypertension at onset	N	18	81.8%	14	66.7%	32	74.4%	1.296	0.255
	Y	4	18.2%	7	33.3%	11	25.6%		
Total		22	100.0%	21	100.0%	43	100.0%		

It was observed that 18.2% patients with SDNS and 33.3% patients with SRNS had hypertension at onset of NS. 25.6% of total study participants had hypertension at onset of NS. The distribution of study participants based on hypertension at onset between two groups of patients was not found to be statistically significant (p>0.05).

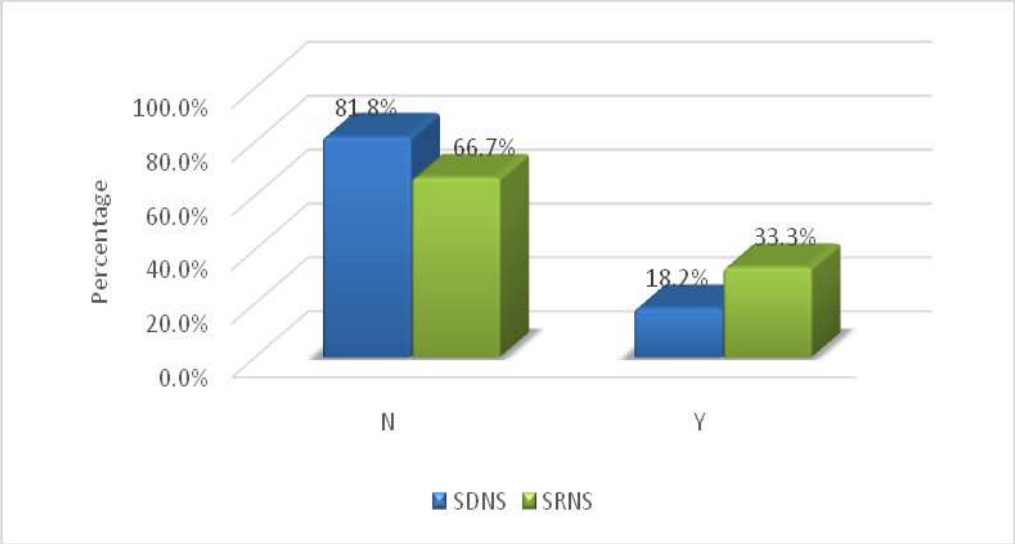


FIGURE NO.5: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON HYPERTENSION AT ONSET OF NS

TABLE NO.6: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON MICROSCOPIC HEMATURIA AT ONSET OF NS

		SDNS		**SRNS**		Total		Chi-square value	p-value
		No. of cases	%age	No. of cases	%age	No. of cases	%age		
Microscopic Haematuria at onset (Y/N)	N	18	81.8%	20	95.2%	38	88.4%	1.883	0.345
	Y	4	18.2%	1	4.8%	5	11.6%		
Total		22	100.0%	21	100.0%	43	100.0%		

It was observed that 18.2% patients with SDNS and 4.8% patients with SRNS had microscopic haematuria at onset of NS. 11.6% of total study participants had microscopic haematuria at onset. The distribution of study participants based on microscopic haematuria at onset of NS between two groups of patients was not found to be statistically significant (p>0.05).

FIGURE NO.6: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON MICROSCOPIC HEMATURIA AT ONSET OF NS

TABLE NO.7: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON NUMBER OF RELAPSE IN LAST ONE YEAR (BEFORE TACROLIMUS)

	No Of Relapse	Last One Year (Before Tacrolimus):		After Starting Tacrolimus (In 12 Months Peroid)	
		No. of cases	%age	No. of cases	%age
SDNS	0	4	18.2%	1	12.5%
	1	2	9.1%	1	12.5%
	2	4	18.2%	3	37.5%
	3	5	22.7%	1	12.5%
	4	7	31.8%	3	37.5%
Total		22	100.0%	8	100.0%

In SDNS group total of 53 relapse events were observed. Most participants (31.8%) had 4 relapses in 1 year before the start of tacrolimus. 22.7% of participants had 3 relapses. 2 and no relapses were seen in 18.2 % of participants. 9.1% of participants had 2 relapses.

No of Relapse	Last One Year (Before Tacrolimus):		After Starting Tacrolimus (In 12 Months Period)		Z	p-value
	Median	IQR	Median	IQR		
SDNS	3	1-4.0	0	0-2.0	3.444	0.002

The median number of relapse in the last one year (before tacrolimus) and after starting TAC was 3 IQR(1-4) and 0 IQR(0-2.0) in patients with SDNS which was statistically significant (p-value <0.05)

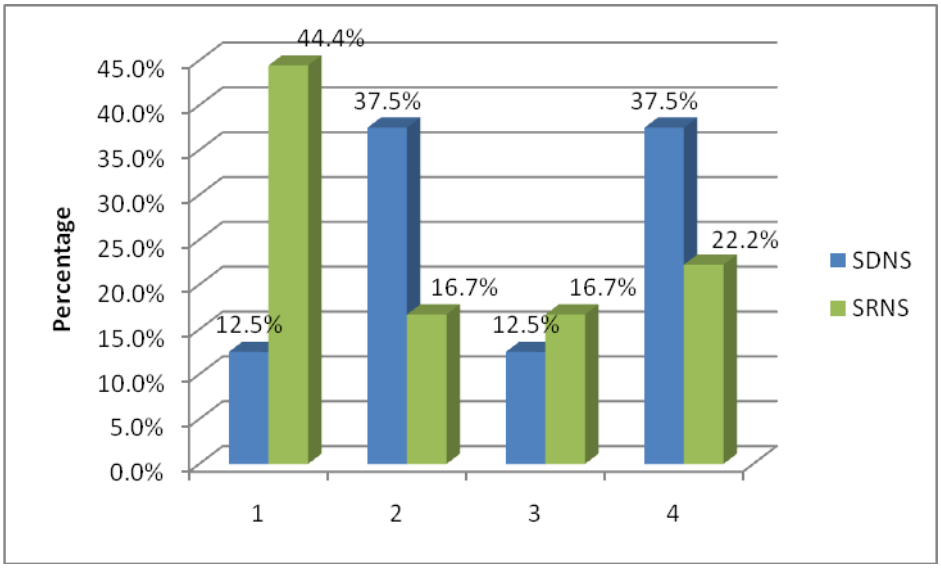


FIGURE NO.7A: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON NUMBER OF RELAPSE IN LAST ONE YEAR (BEFORE TACROLIMUS)

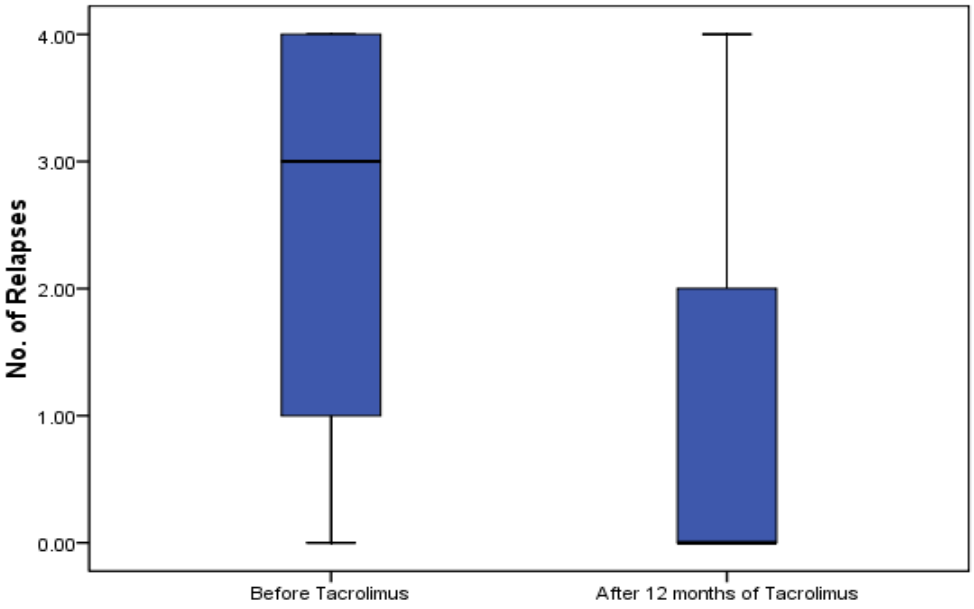


FIGURE NO.7B: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON NUMBER OF RELAPSE IN LAST ONE YEAR (BEFORE TACROLIMUS)

TABLE NO.8: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON PRIOR DRUG THERAPY

		SDNS		SRNS		Total		Chi-square value	p-value
		No. of cases	%age	No. of cases	%age	No. of cases	%age		
Only steroids	Y	10	45.5%	16	76.2%	26	60.5%	4.246	0.039
	N	12	54.5%	5	23.8%	17	39.5%		
Levamisole	N	14	63.6%	21	100.0%	35	81.4%	9.3818	0.002
	Y	8	36.4%	0	0.0%	8	18.6%		
Cyclophosphamide	N	14	63.6%	20	95.2%	34	79.1%	6.484	0.021
	Y	8	36.4%	1	4.8%	9	20.9%		
Mycophenolate	N	13	59.1%	20	95.2%	33	76.7%	7.866	0.009
	Y	9	40.9%	1	4.8%	10	23.3%		
Cyclosporine	N	20	90.9%	16	76.2%	36	83.7%	1.708	0.24
	Y	2	9.1%	5	23.8%	7	16.3%		
Total		22	100.0%	21	100.0%	43	100.0%		

45.5% of patients with SDNS and 76.2% of patients with SRNS were only on steroids. Upon statistical analysis, there were significantly greater number of patients only on steroids in SDNS group as compared to SRNS ($p<0.05$).
36.4% of patients with SDNS were on levamisole.

36.4% of patients with SDNS and 4.8% of patients with SRNS were on Cyclophosphamide. Upon statistical analysis, there were significantly greater number of patients on Cyclophosphamide in SDNS group as compared to SRNS ($p<0.05$).

40.9 % of patients with SDNS and 4.8% of patients with SRNS were on mycophenolate. Upon statistical analysis, there were significantly greater number of patients on mycophenolate in SDNS group as compared to SRNS ($p<0.05$).

9.1% of patients with SDNS and 23.8% of patients with SRNS were on cyclosporine. Upon statistical analysis, this was not found to be significant ($p>0.05$).

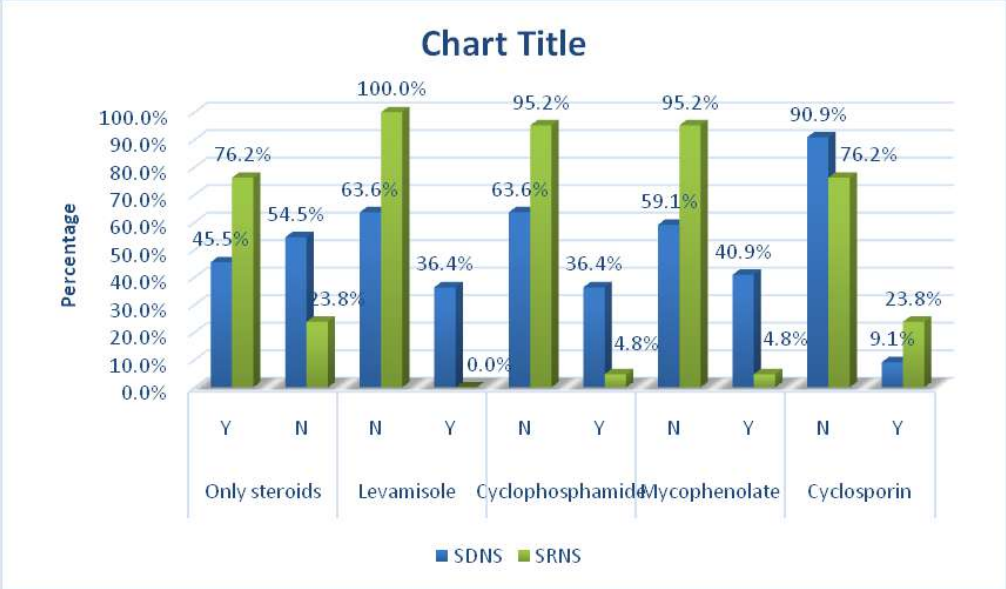


FIGURE NO.8: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON PRIOR DRUG THERAPY

TABLE NO.9: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON AGE OF ONSET AND AGE AT START OF TACROLIMUS

	SDNS		SRNS		Z	p-value	SDNS		SRNS	
	Median	IQR	Median	IQR			Mean	SD	Mean	SD
Age at Onset of NS (Years)	3.5	1.575-5	4.0	2.7-4.75	-0.817	0.414	3.7	2.5	3.9	2.0
Age at Start Of Tacrolimus (Years)	6.5	4.75-8.5	4.9	3.3-6.25	-1.750	0.080	6.6	2.9	5.4	3.0
Duration Of NS (Months)	18.0	7-42.5	7.0	2-19	-1.935	0.049	28.1	28.0	20.0	37.2

The median age of onset in patients with SDNS and SRNS was found to be 3.5 and 4 years respectively. Upon statistical analysis, this was not found to be significant (p>0.05).

The median age at start of tacrolimus in patients with SDNS and SRNS was found to be 6.5 and 4.9 years respectively. Upon statistical analysis, this was not found to be significant (p>0.05).

The median duration of NS in patients was greater in SDNS than in SRNS patients, 18 and 7 months respectively. Upon statistical analysis, this was found to be significant (p>0.05).

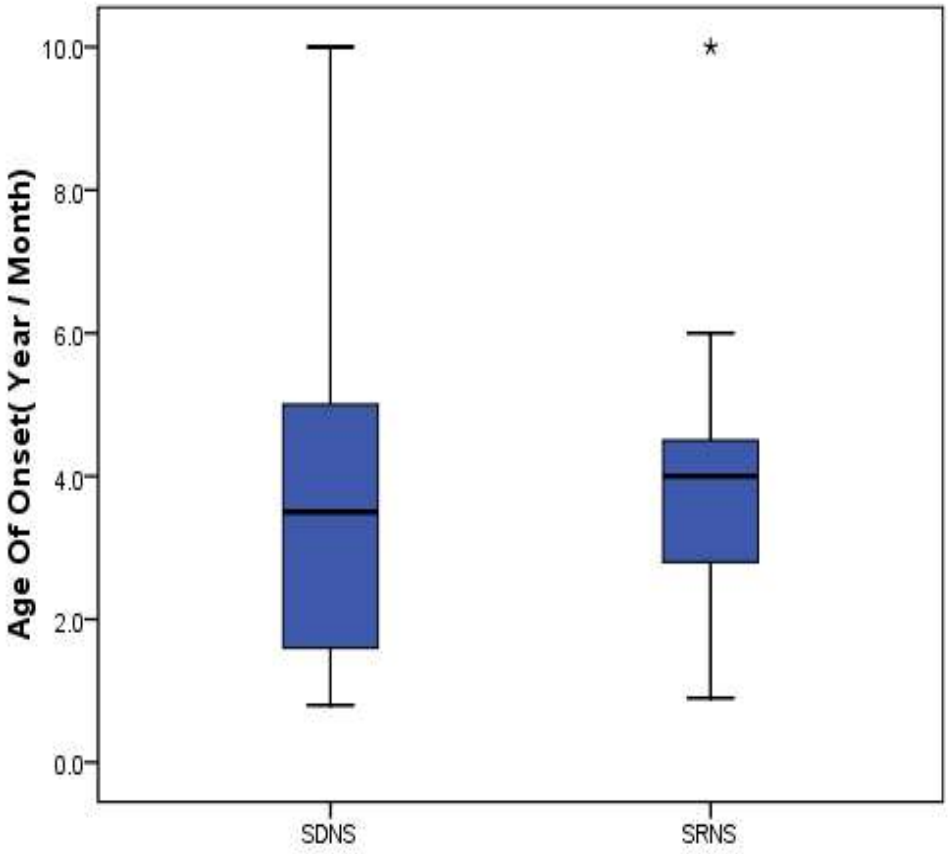


FIGURE NO.9A: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON AGE OF ONSET OF NS

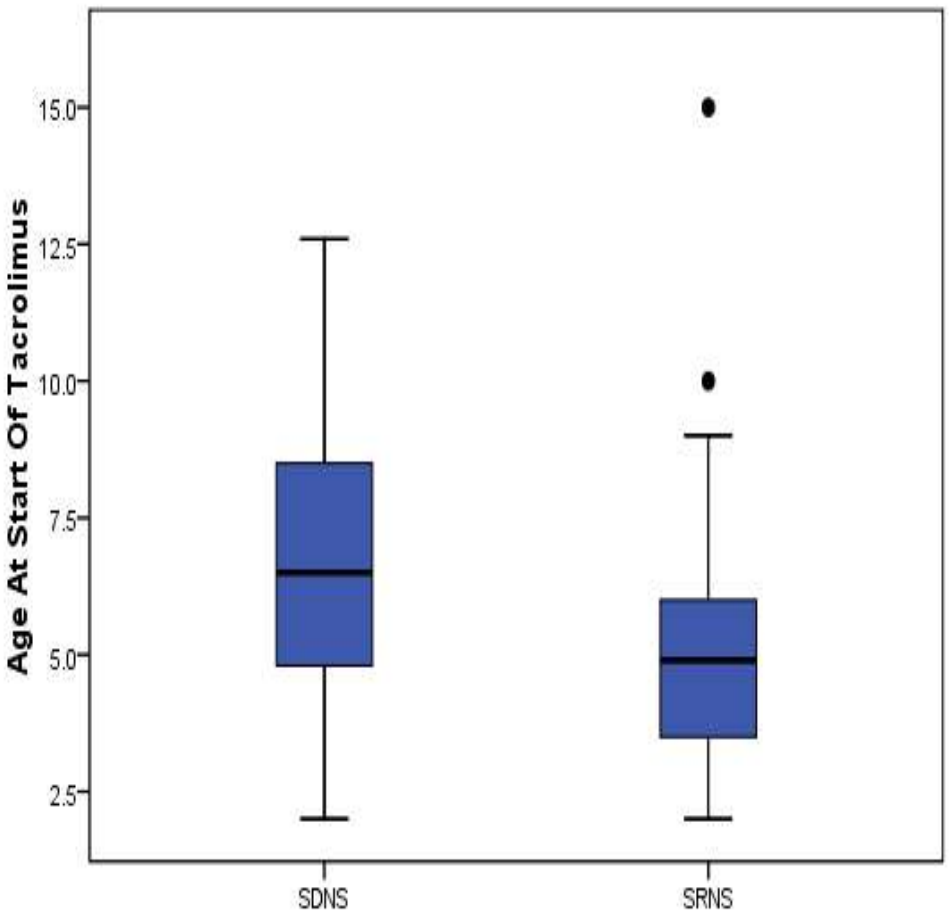


FIGURE NO.9B: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON AGE AT START OF TACROLIMUS

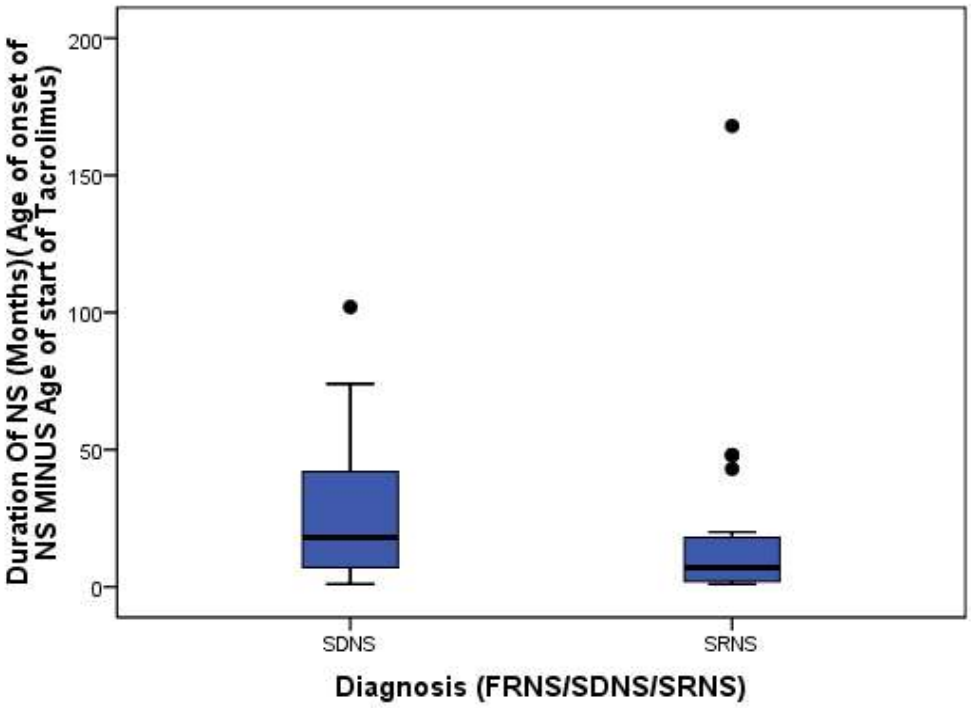


FIGURE NO.9C: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON DURATION OF NS

TABLE NO.10: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON STATUS AT START OF TACROLIMUS

		SDNS		SRNS		Total		Chi-square value	p-value
		SDNS	SDNS	SRNS	SRNS	No. of cases	%age		
Status Of Patient At Start Of Tacrolimus	CR	22	100.0%	0	0.0%	22	51.2%	43	0.001
	PR	0	0.0%	1	4.8%	1	2.3%		
	NR	0	0.0%	20	95.2%	20	46.5%		
Total		22	100.0%	21	100.0%	43	100.0%		

CR = Complete remission

PR = Partial remission

NR = No remission

Allpatients with SDNS (100%) were in complete remission. 95.2% of patients with SRNS showed no remission and 4.8% showed partial remission. This was found to be statistically significant ($p<0.05$).

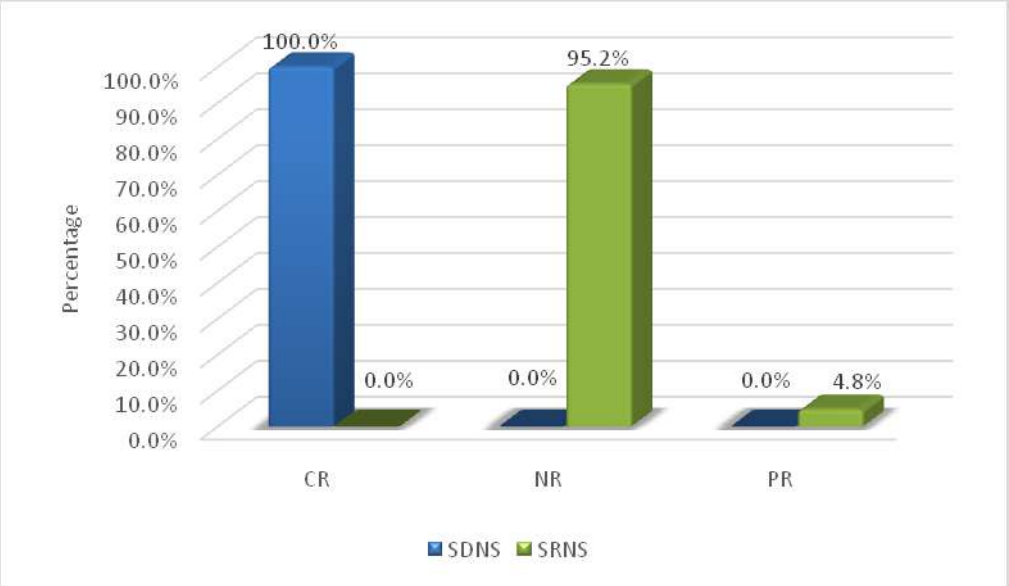


FIGURE NO.10: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON STATUS AT START OF TACROLIMUS

TABLE NO.11: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON STEROID SIDE EFFECT AT START OF STUDY

	SDNS		**SRNS**		Total		Chi-square value	p-value
	No. of cases	%age	No. of cases	%age	No. of cases	%age		
Cumulative Steroid Toxicity	15	68.2%	17	81.0%	32	74.4%	0.92	0.337
Cushingoid	7	31.8%	7	33.3%	14	32.6%	0.001	0.916
Short Stature	5	22.7%	4	19.0%	9	20.9%	0.088	0.767
Hypertension	8	36.4%	11	52.4%	19	44.2%	1.118	0.290
Obesity	9	40.9%	5	23.8%	14	32.6%	1.43	0.232
Behaviour	1	4.5%	0	0.0%	1	2.3%	0.977	0.323
Cataract	0	0.0%	0	0.0%	0	0.0%		

Cumulative steroid toxicity was seen in 74.4% of study participants. 68.2% in SDNS group and 81% in SRNS group had steroid toxicity.Cushingoid features was seen in 32.6% of study participants. 31.8% in SDNS group and 33.3% in SRNS group had cushingoid features.

Short stature was seen in 20.9% of study participants. 22.7% in SDNS group and 19% in SRNS group was observed had short stature.

Hypertension was more in patients with SRNS as compared to SDNS group 52.4% and 36.4% respectively. A total of 44.2% had hypertension secondary to use of steroid (Prednisolone)

Obesity was seen in 27.9% of study participants. 31.8% in SDNS group and 23.8% in SRNS group were obese. Behaviour changes was noted in 4.5% (1 case) in SDNS group.

The distribution of study participants based on these clinical features between two groups of patients was not found to be statistically significant (p>0.05).

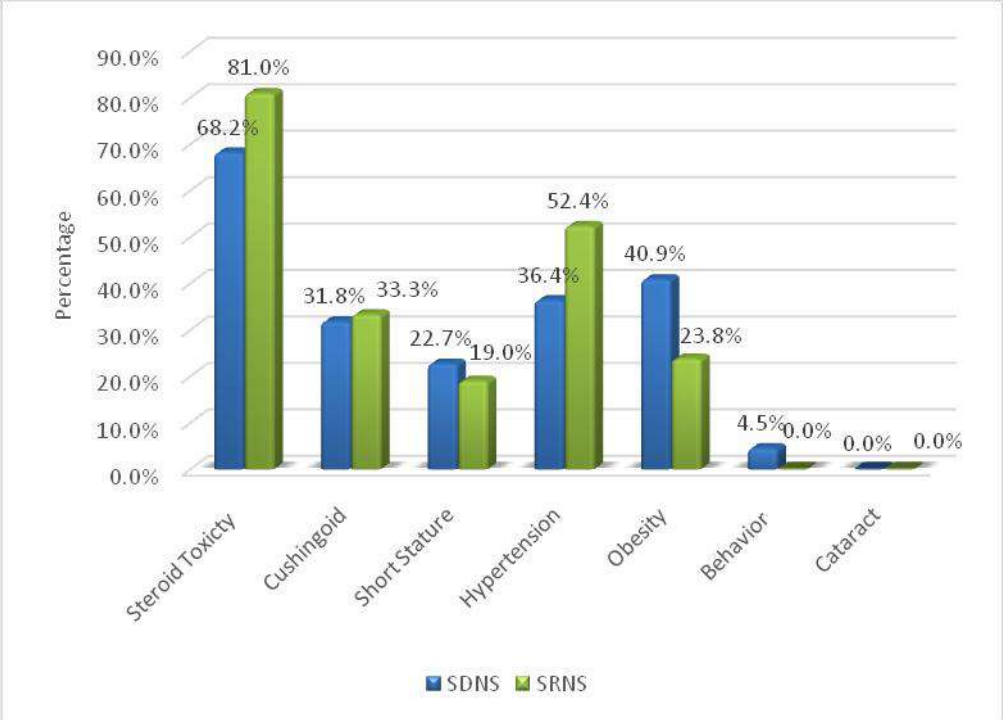


FIGURE NO.11: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON STEROID SIDE EFFECT AT START OF STUDY

TABLE NO.12 : DISTRIBUTION OF STUDY PARTICIPANTS BASED ON RENAL BIOPSY FINDINGS

		SDNS		**SRNS**		Total		Chi-square value	p-value
		No. of cases	%age	No. of cases	%age	No. of cases	%age		
Renal Biopsy Finding	FSGS	1	4.5%	3	14.3%	4	9.3%	1.222	0.543
	MCNS	5	22.7%	4	19.0%	9	20.9%		
	NOT DONE	16	72.7%	14	66.7%	30	69.8%		
Total		22	100.0%	21	100.0%	43	100.0%		

72.7% of patients with SDNS and 66.7% of patients with SRNS did not undergo renal biopsy. Focal segmental glomerulosclerosis (FSGS) was seen in 4.5% patients with SDNS and 14.3% patients with SRNS. Minimal change nephrotic syndrome (MCNS) was seen in 22.7% patients with SDNS and 19% patients with SRNS. The distribution of study participants based renal biopsy findings between two groups of patients was not found to be statistically significant (p>0.05).

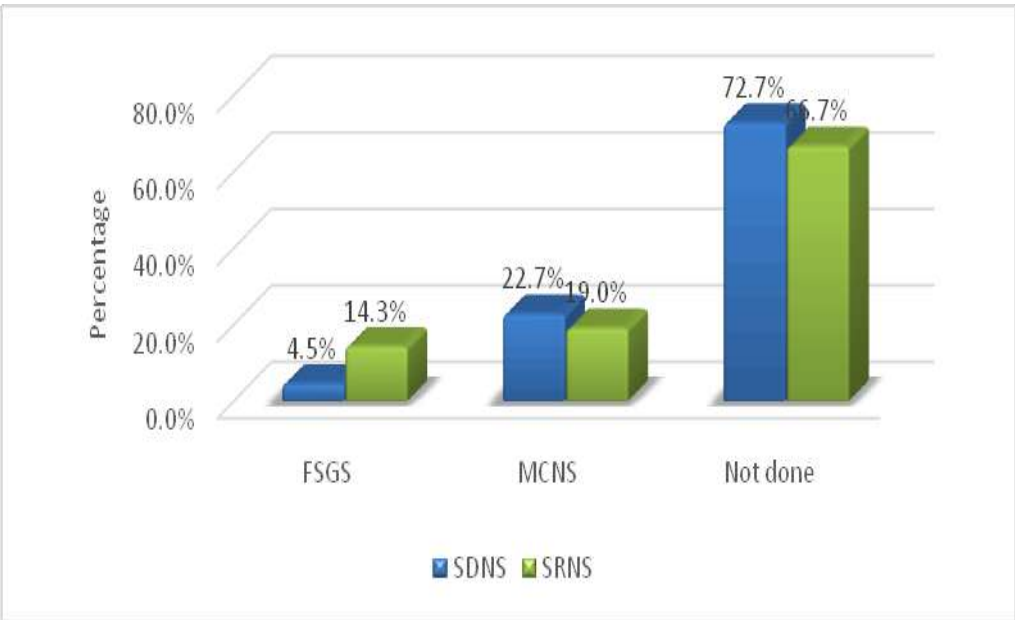


FIGURE NO.12: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON RENAL BIOPSY FINDINGS

TABLE NO. 13: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON ASSOCIATED MEDICATION USED

		SDNS		SRNS		Total		Chi-square value	p-value
Associated Medications		Cases	%	Cases	%	Cases	%		
ENVAS	Y	19	86.4%	17	81.0%	36	83.7%	0.231	0.631
ELTROXIN	Y	0	0.0%	1	4.8%	1	2.3%	0.978	0.423

Anti-hypertensive (Envas) was administered to 86.4% of patients with SDNS and 81% of patients with SRNS. The distribution of study participants based on anti-hypertensive (Envas) usage between two groups of patients was not found to be statistically significant (p>0.05).
Hypothyroidism was seen in 1 patient with SRNS who was administered Eltroxin. No patients in SDNS group had HypothyroidismThe distribution of study participants based on Eltroxin usage between two groups of patients was not found to be statistically significant (p>0.05).

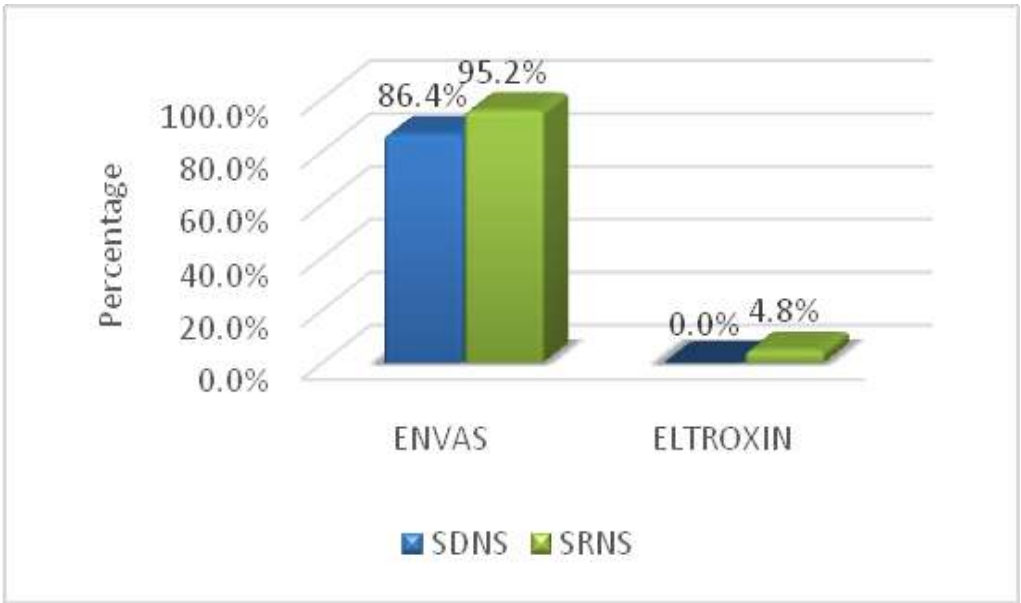


FIGURE NO.13: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON ASSOCIATED MEDICATION USED

TABLE NO.14: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON STARTING DOSE OF TACROLIMUS

	SDNS		SRNS		Z	p-value
	Median	IQR	Median	IQR		
STARTING DOSE (Mg/Kg)	0.1	0.06-0.10	0.1	0.07-0.11	-0.850	0.395

Median starting dose of both groups was 0.1 mg/kg with IQR of 0.0575-0.105 and 0.075-0.11 of SDNS and SRNS participants. The distribution of study participants based on starting dose between two groups of patients was not found to be statistically significant (p>0.05).

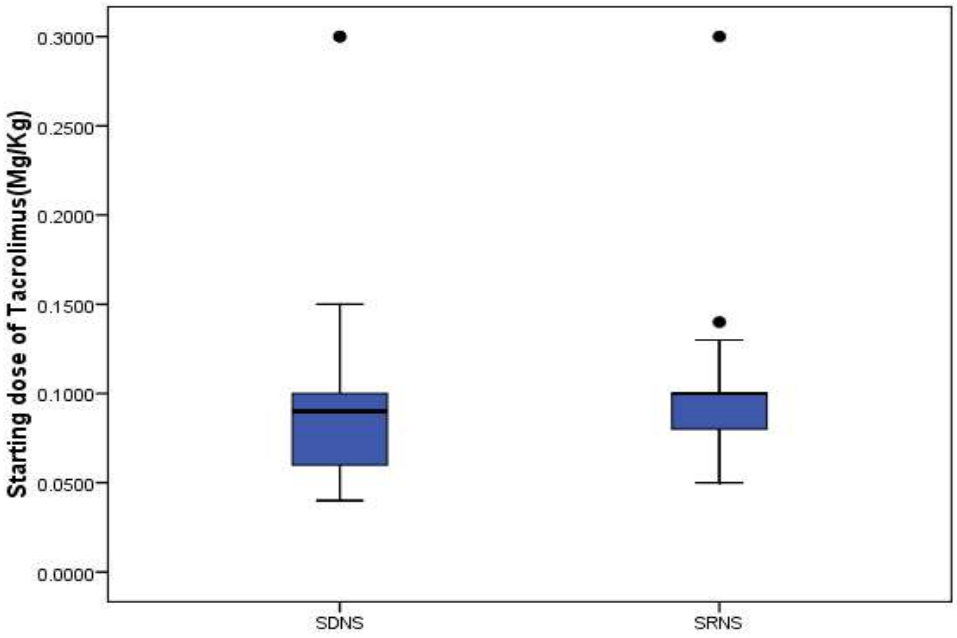


FIGURE NO.14: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON STARTING DOSE OF TACROLIMUS

TABLE NO.15: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON SERUM ALBUMIN LEVELS

	SDNS		SRNS		Z	p-value
Serum albumin	Median	IQR	Median	IQR		
at start	2.78	2.6-3.1	1.64	1.38-1.89	-5.617	0.000
at 1 month	2.95	2.76-3.20	2.56	2.20-3.15	-2.116	0.034
at 6 month	3.20	3-3.45	2.90	2.66-3.28	-2.022	0.043
at 12 month	3.44	3.1-4.065	2.90	2.3-3.5	-2.763	0.006

The median serum albumin levels at start of patients with SDNS and SRNS was found to be 2.78 and 1.64 respectively. The difference in serum albumin levels at start of patients between two groups was found to be statistically significant ($p<0.05$).

The median serum albumin levels at 1 month of patients with SDNS and SRNS was found to be 2.95 and 2.56 respectively. The difference in serum albumin levels at 1 month of patients between two groups was found to be statistically significant ($p<0.05$).

The median serum albumin levels at 6 months of patients with SDNS and SRNS was found to be 3.20 and 2.90 respectively. The difference in serum albumin levels at 6 months of patients between two groups was found to be statistically significant ($p<0.05$).

The median serum albumin levels at 12 months of patients with SDNS and SRNS was found to be 3.44 and 2.90 respectively. The difference in serum albumin levels at 6 months of patients between two groups was found to be statistically significant ($p<0.05$).

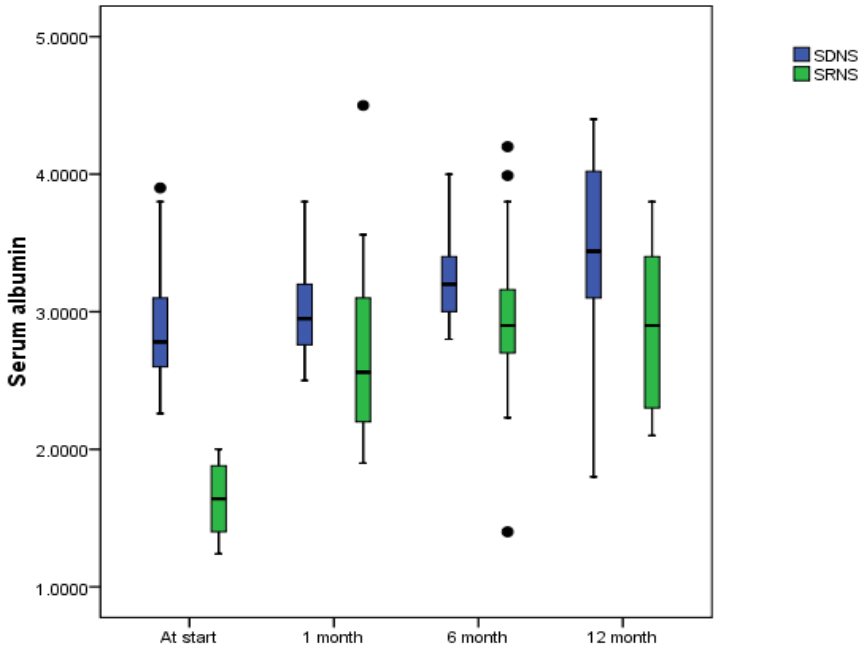


FIGURE NO.15: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON SERUM ALBUMIN LEVELS

TABLE NO.16: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON SERUM CREATININE LEVELS

	SDNS		SRNS		Z	p-value
Serum creatinine	Median	IQR	Median	IQR		
at start	0.37	0.3375-0.4	0.32	0.28-0.41	-1.303	0.193
at 1 month	0.38	0.355-0.42	0.33	0.29-0.4	-1.658	0.097
at 6 months	0.38	0.3375-0.4	0.31	0.29-0.40	-1.183	0.237
at 12 months	0.38	0.36-0.4	0.32	0.21-0.4	-1.903	0.057

The median serum creatinine levels at start of patients with SDNS and SRNS was found to be 0.37 and 0.32 respectively. The difference in serum creatinine levels at start of patients between two groups was not found to be statistically significant ($p>0.05$).

The median serum creatinine levels at 1 month of patients with SDNS and SRNS was found to be 0.38 and 0.33 respectively. The difference in serum creatinine levels at 1 month of patients between two groups was not found to be statistically significant ($p>0.05$).

The median serum creatinine levels at 6 months of patients with SDNS and SRNS was found to be 0.38 and 0.31 respectively. The difference in serum creatinine levels at 6 months of patients between two groups was not found to be statistically significant ($p>0.05$).

The median serum creatinine levels at 12 months of patients with SDNS and SRNS was found to be 0.38 and 0.32 respectively. The difference in serum creatinine levels at 12 months of patients between two groups was not found to be statistically significant ($p>0.05$).

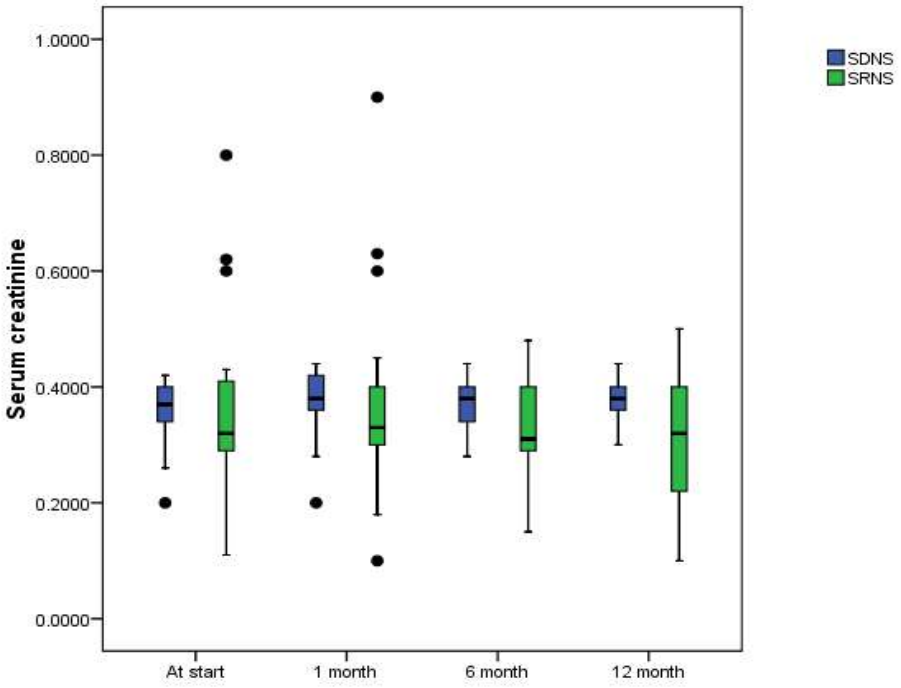


FIGURE NO.16: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON SERUM CREATININE LEVELS

TABLE NO.17: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON TACROLIMUS LEVELS

	SDNS		SRNS		Z	p-value
TACROLIMUS LEVELS	Median	IQR	Median	IQR		
at 1 month	3.8	1.99-7.23	1.8	1.52-2.81	-1.987	0.047
at 3 month	3.9	3.2-7.28	3.0	1.80-3.86	-1.914	0.056
at 6 month	4.5	3.08-5.38	3.4	2.23-4.63	-1.539	0.124
at 9 month	3.4	2.44-4.66	3.6	2.19-5.24	-0.194	0.846
at 12 month	4.7	3.15-6.22	4.2	3.36-5.72	-0.257	0.797

The median tacrolimus levels at 1 month of patients with SDNS and SRNS was found to be 3.8 and 1.8 respectively. The difference in tacrolimus levels at 1 month between patients of two groups was found to be statistically significant ($p<0.05$).

The median tacrolimus levels at 3 months of patients with SDNS and SRNS was found to be 3.9 and 3.0 respectively. The difference in tacrolimus levels at 3 months between patients of two groups was not found to be statistically significant ($p>0.05$).

The median tacrolimus levels at 6 months of patients with SDNS and SRNS was found to be 4.5 and 3.4 respectively. The difference in tacrolimus levels at 6 months between patients of two groups was not found to be statistically significant ($p>0.05$).

The median tacrolimus levels at 9 months of patients with SDNS and SRNS was found to be 3.4 and 3.6 respectively. The difference in tacrolimus levels at 9 months between patients of two groups was not found to be statistically significant ($p>0.05$).

The median tacrolimus levels at 12 months of patients with SDNS and SRNS was found to be 4.7 and 4.2 respectively. The difference in tacrolimus levels at 12 months between patients of two groups was not found to be statistically significant (p>0.05).

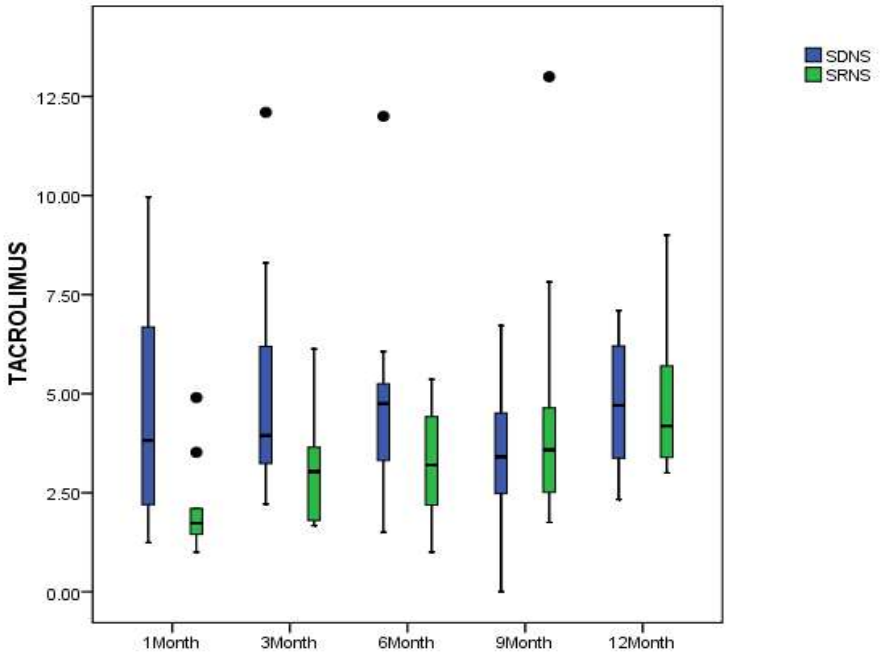


FIGURE NO.17: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON TACROLIMUS LEVELS

TABLE NO.18: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON OVERALL TACROLIMUS LEVELS

	SDNS		SRNS		Z Score	p-value
	Median	IQR	Median	IQR		
Overall Tacrolimus Levels	4.05	3.27-5.77	3.40	2.85-4.15	-2.176	0.030

The median tacrolimus levels of patients with SDNS and SRNS was found to be 4.05 and 3.4 respectively. The difference in tacrolimus levels between patients of two groups was found to be statistically significant ($p<0.05$).

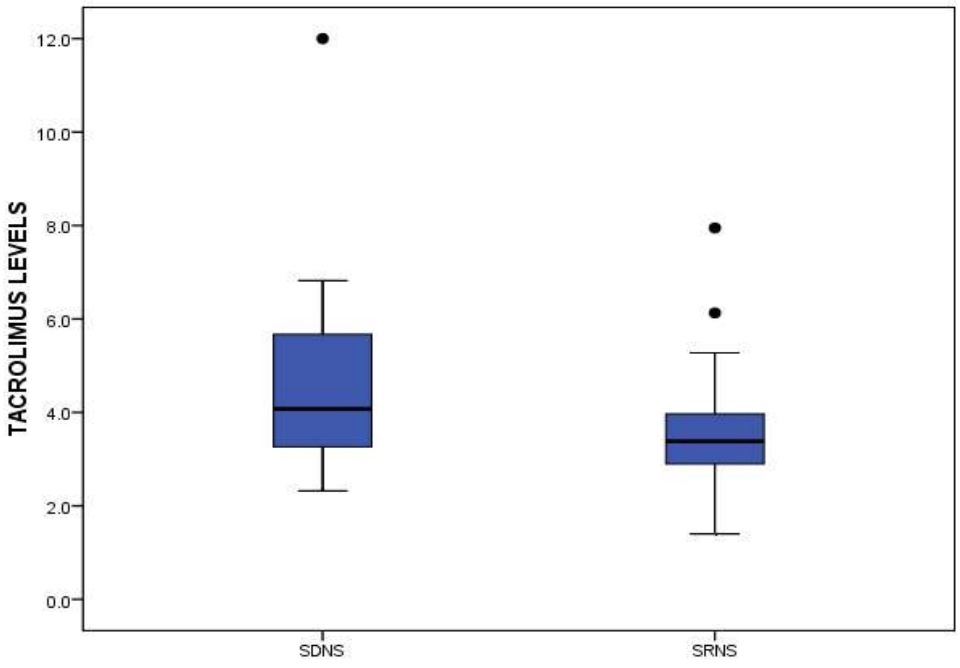


FIGURE NO.18: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON OVERALL TACROLIMUS LEVELS

TABLE NO.19: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON DURATION OF TACROLIMUS GIVEN

	SDNS		SRNS		Z	p-value
Duration Of Tacrolimus Given	Median	IQR	Median	IQR		
Months	15.5	13.75-36	25.0	12.5-30	-0.253	0.800

The median duration for which tacrolimus was given to patients with SDNS and SRNS was found to be 15.5 and 25 months respectively. The difference in median duration for which tacrolimus was given between patients of two groups was not found to be statistically significant (p>0.05).

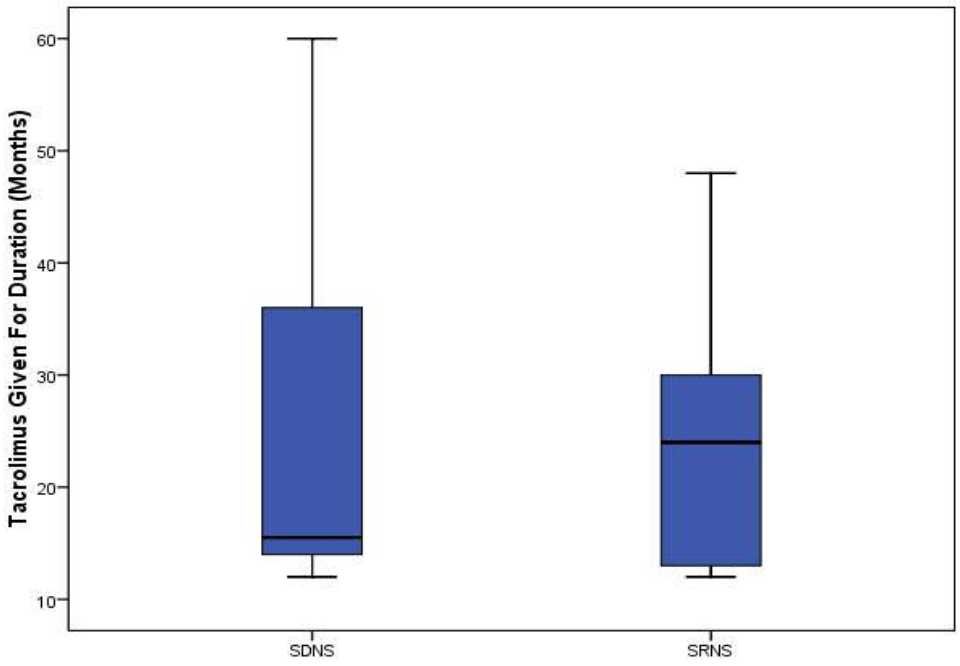


FIGURE NO.19: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON DURATION OF TACROLIMUS GIVEN

TABLE NO.20: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON NUMBER OF TIMES TACROLIMUS LEVEL DONE

		SDNS		SRNS		Total		Chi-square value	p-value
		Cases	%	Cases	%	Cases	%		
No. of times TAC levels done	1	8	36.4%	4	19.0%	12	27.9%	3.274	0.513
	2	2	9.1%	3	14.3%	5	11.6%		
	3	2	9.1%	5	23.8%	7	16.3%		
	4	3	13.6%	4	19.0%	7	16.3%		
	5	7	31.8%	5	23.8%	12	27.9%		
Total		22	100.0%	21	100.0%	43	100.0%		

	SDNS		SRNS		Z	p-value
	Median	IQR	Median	IQR		
No. of times Tacrolimus level done	3.00	1-5.0	3.00	2-5.0	-0.337	0.736

In SDNS group 36.4% patients had tacrolimus level done only once in 12 month study period. 9.1% patients had done TAC levels 2 and 3 times. 13.6% patients had done TAC levels 4 times and 31.8% had done TAC levels 5 times or more.

In SRNS group 19% of patients had done TAC level only once. 14.3% had done TAC level 2 times, 23.8% patients had done TAC level three times, 19% patients had done TAC levels 4 times. 23.8% had done TAC levels five times.

The median number of times tacrolimus levels were done was 1 and 2 respectively in patients with SDNS and SRNS. Upon statistical analysis, this was not found to be significant (p>0.05).

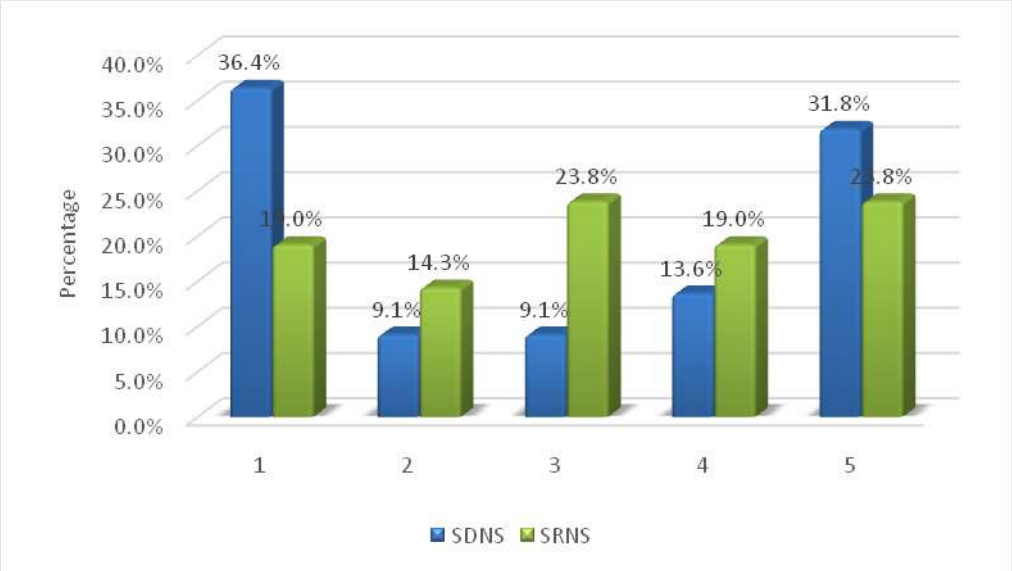


FIGURE NO.20A: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON NUMBER OF TIMES TACROLIMUS LEVEL DONE

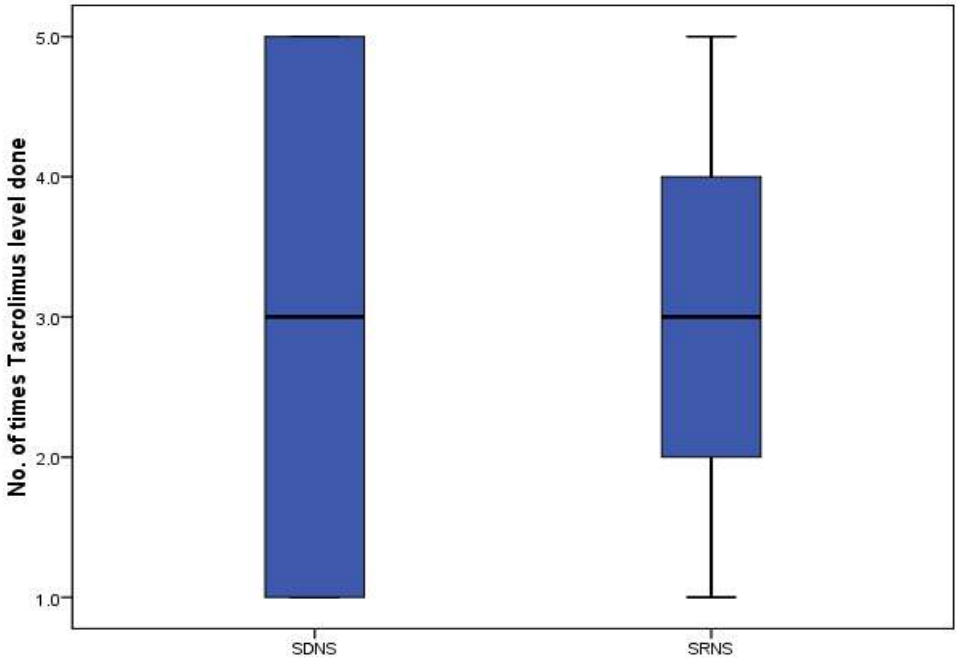


FIGURE NO.20B: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON NUMBER OF TIMES TACROLIMUS LEVEL DONE

TABLE NO.21: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON SIDE EFFECTS OF TACROLIMUS

	SDNS		SRNS		Total		Chi-square value	p-value
	No. of cases	%age	No. of cases	%age	No. of cases	%age		
Hypertension	5	22.7%	13	61.9%	18	41.9%	6.776	0.014
Diarrhea	1	4.5%	4	19.0%	5	11.6%	2.199	0.185
UTI	1	4.5%	3	14.3%	4	9.3%	1.208	0.345
Acute Tonsilitis	0	0.0%	1	4.8%	1	2.3%	0.978	0.423
Reversible Nephropathy	1	4.5%	0	0.0%	1	2.3%	0.977	0.323
Chicken Pox	1	4.5%	0	0.0%	1	2.3%	0.977	0.323
Pyoderma	1	4.5%	0	0.0%	1	2.3%	0.977	0.323
Pneumonia	1	4.5%	2	9.5%	3	7.0%	4.210	0.240
Bronchiolitis	1	4.5%	1	4.8%	2	4.7%		
Hyperkalemia	0	0.0%	0	0.0%	0	0.0%		
Seizure	0	0.0%	0	0.0%	0	0.0%		

	SDNS		SRNS		Total		Chi-square value	p-value
	No. of cases	%age	No. of cases	%age	No. of cases	%age		
Increase Blood Sugar	0	0.0%	0	0.0%	0	0.0%		
Increase OT/ PT	0	0.0%	0	0.0%	0	0.0%		
Hypertrichosis	0	0.0%	0	0.0%	0	0.0%		
Gingival Hyperplasia	0	0.0%	0	0.0%	0	0.0%		
Acne	0	0.0%	0	0.0%	0	0.0%		

Hypertension was seen in 22.7% patients with SDNS and 61.9% patients with SRNS patients. The distribution of study participants based on hypertension between two groups of patients was found to be statistically significant (p>0.05). Chicken Pox and Pyoderma was seen in 1 patient of SDNS group (4.5%). Diarrhea, UTI, reversible nephropathy, pneumonia and bronchiolitis were seen in 4.5% patients each with SDNS. Hypertension, diarrhea, UTI, reversible nephropathy, skin infections, pneumonia and bronchiolitis were seen in 41.9%, 11.6%, 9.3%, 2.3%, 4.7%, 7.0% and 4.7% patients with SRNS respectively. Acute tonsillitis was seen in 4.8% patients with SRNS and not observed in any of the patients with SDNS.

The distribution of study participants based on side effects of tacrolimus between two groups of patients was not found to be statistically significant (p>0.05) except for hypertension (p<0.05).

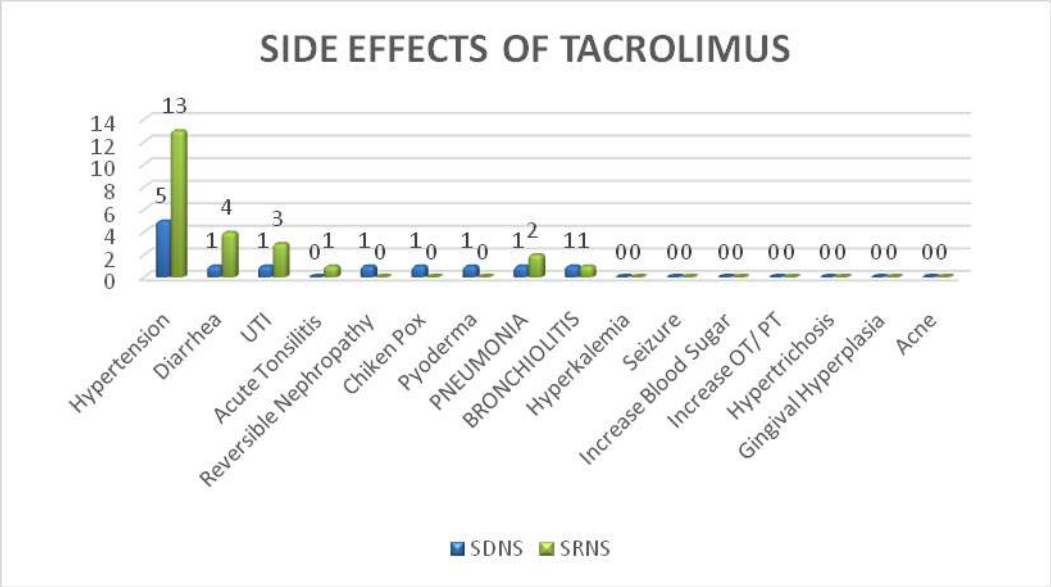


FIGURE NO.21: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON SIDE EFFECTS OF TACROLIMUS

TABLE NO.22: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON STATUS AT 6 MONTHS

		SDNS		SRNS		Total		Chi-square value	p-value
		No. of cases	%age	No. of cases	%age	No. of cases	%age		
At 6 Months	CR	19	86.4%	9	42.9%	28	65.1%	10.154	0.006
	PR	2	9.1%	3	14.3%	5	11.6%		
	NR	1	4.5%	9	42.9%	10	23.3%		
Total		22	100.0%	21	100.0%	43	100.0%		

At 6 months, complete remission, partial remission and no remission was seen in 86.4%, 9.1% and 4.5% patients with SDNS respectively. 95.5% patients in SDNS were responder and 4.5% had no response to TAC.

Complete remission, partial remission and no remission was seen in 42.9%, 14.3% and 42.9% patients with SRNS respectively at 6 months.57.2% patients in SRNS were responder and 42.8% had no response to TAC.

The distribution of study participants based on response status at 6 months between two groups of patients was found to be statistically significant ($p<0.05$).

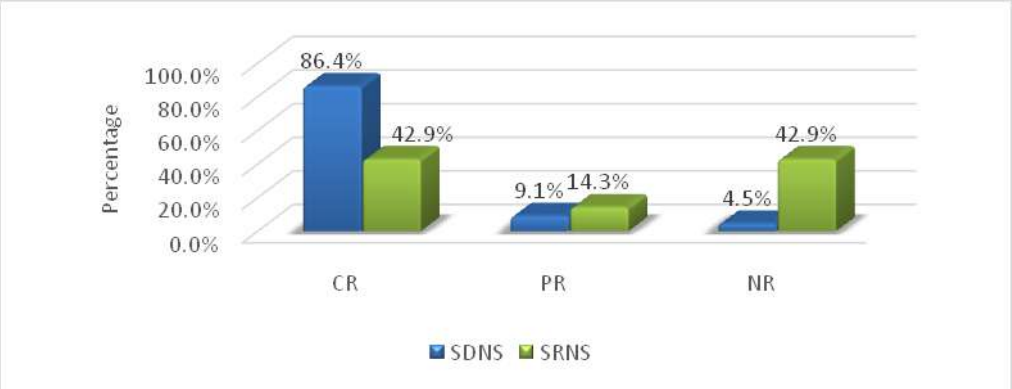


FIGURE NO.22A: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON STATUS AT 6 MONTHS

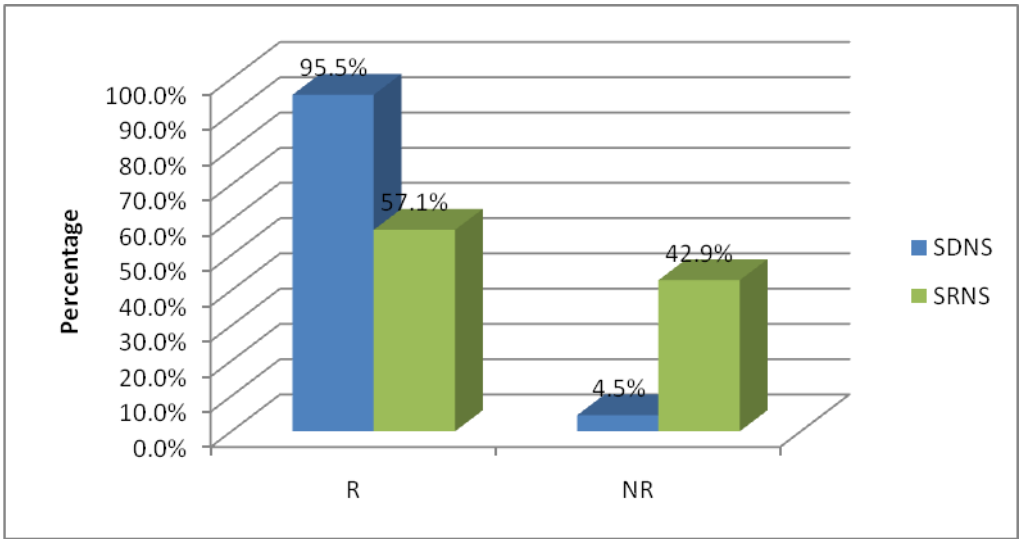


FIGURE NO.22B: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON STATUS AT 6 MONTHS

TABLE NO.23: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON STATUS AT 12 MONTHS

		SDNS		SRNS		Total		Chi-square value	p-value
		No. of cases	%age	No. of cases	%age	No. of cases	%age		
At 12 months	CR	20	90.9%	12	57.1%	32	74.4%	6.55	0.038
	PR	1	4.5%	3	14.3%	4	9.3%		
	NR	1	4.5%	6	28.6%	7	16.3%		
Total		22	100.0%	21	100.0%	43	100.0%		

At 12 months, complete remission, partial remission and no remission was seen in 90.9%, 4.5% and 4.5% patients with SDNS respectively. 95.4% patients in SDNS were responder and 4.5% had no response to TAC.

Complete remission, partial remission and no remission was seen in 57.1%, 14.3% and 28.6% patients with SRNS respectively at 12 months.

71.4% patients in SRNS were responder (CR+PR) and 28.6% had no response to TAC.

The distribution of study participants based on response status at 12 months between two groups of patients was found to be statistically significant ($p<0.05$).

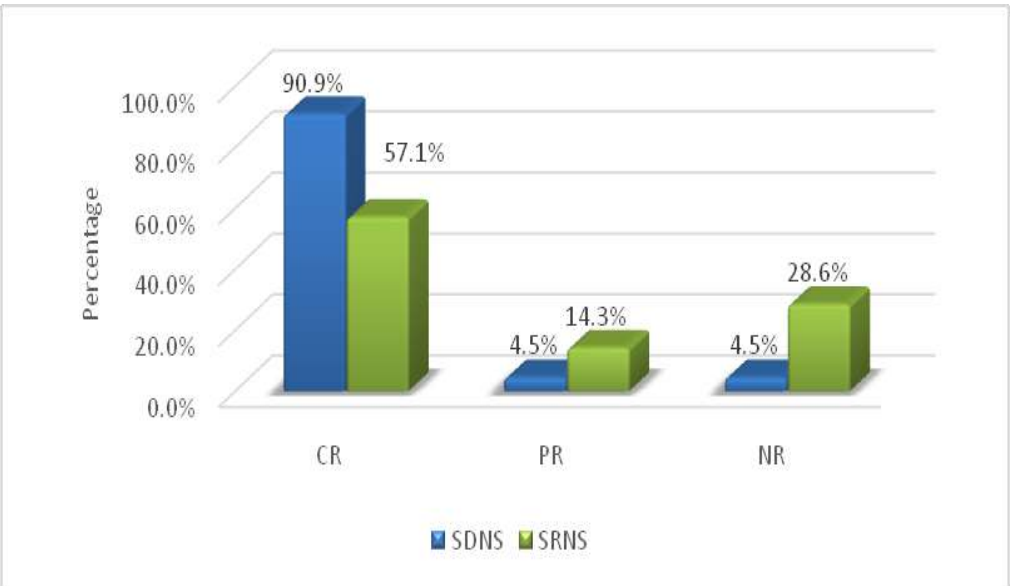


FIGURE NO.23A: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON STATUS AT 12 MONTHS

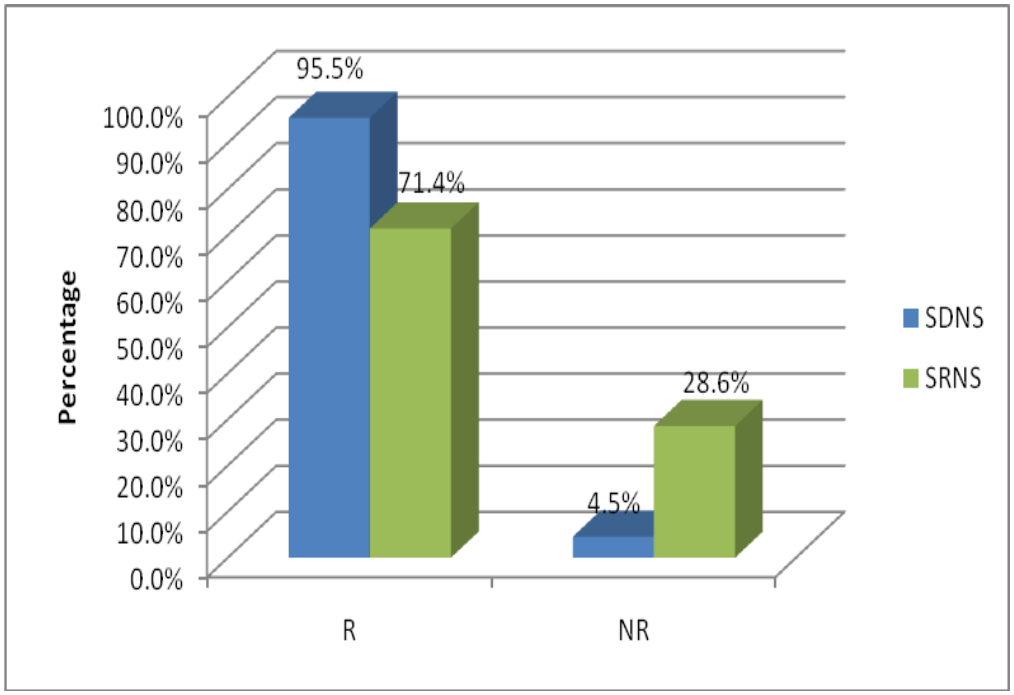


FIGURE NO.23B: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON STATUS AT 12 MONTHS

TABLE NO.24: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON STEROID DEPENDENT DOSE (BEFORE AND AFTER TAC)

Steroid Dependent Dose (Mg/Kg/Day)	at start		at 12 months		Z	p-value
	Median	IQR	Median	IQR		
SDNS	1.4	1.23-1.5	0.55	0.45-0.93	-2.201	0.028

The median dependent dose and steroid dependent dose was 1.4 IQR(1.23-1.5) and 0.55 IQR (0.45-0.93) mg/kg/day respectively. The difference was -0.85mg/kg. Upon statistical analysis, this was found to be significant ($p<0.05$).

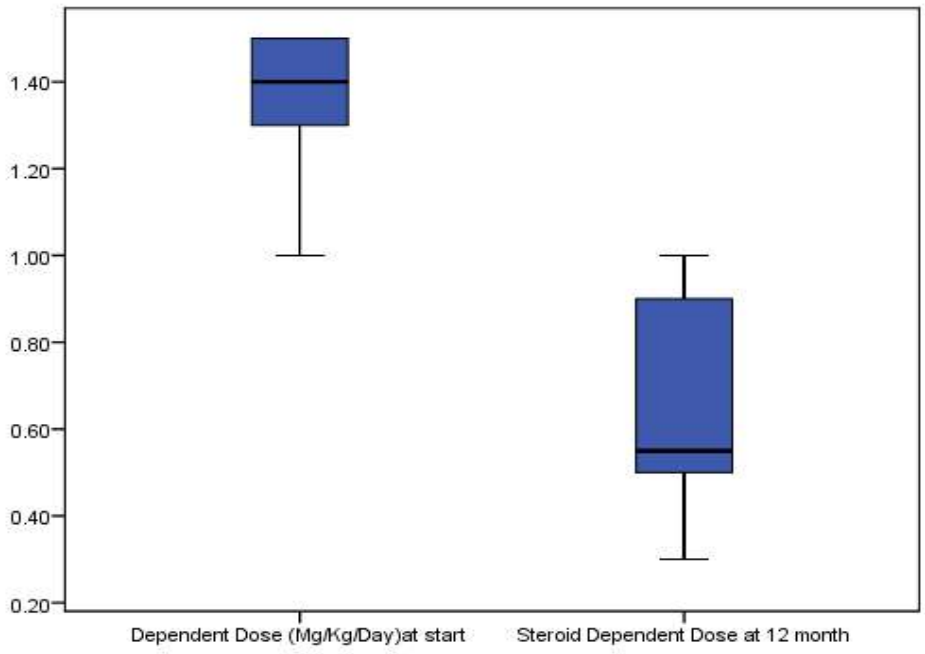


FIGURE NO.24: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON DEPENDENT DOSE

TABLE NO 25: COMPARISON OF INCIDENCE RELAPSE RATE BEFORE AND AFTER TACROLIMUS ADMINISTRATION IN SDNS GROUP

No Of Relapse		
SDNS	Before Tacrolimus:	after Tacrolimus (In 12 Months Period)
No. of Relapse	53	22
Incidence relapse rate	2.4	1

Incidence relapse rate seen in SDNS before and after tacrolimus in 12 month was 2.4 and 1 Relapse-Person-Year respectively. The difference of Incidence relapse rate was -1.4.

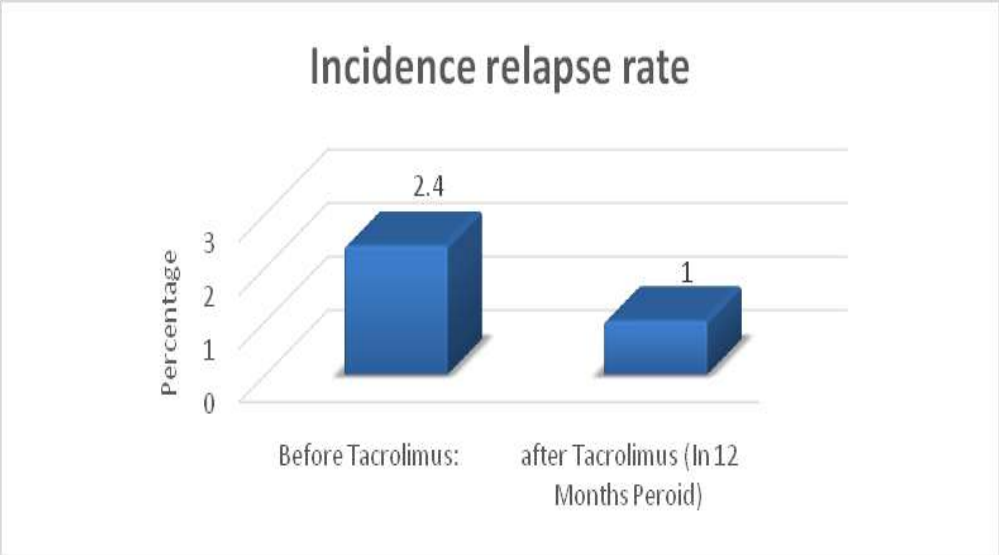


FIGURE NO 25: COMPARISON OF INCIDENCE RELAPSE RATE BEFORE AND AFTER TACROLIMUS ADMINISTRATION IN SDNS GROUP

TABLE NO.26: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON DISCONTINUATION OF STEROIDS

		SDNS		SRNS		Total		Chi-square value	p-value
		No. of cases	%	No. of cases	%	No. of cases	%age		
Off Steroids	N	6	27.3%	15	71.4%	21	48.8%	8.384	0.006
	Y	16	72.7%	6	28.6%	22	51.2%		
Total		22	100.0%	21	100.0%	43	100.0%		

72.7% patients with SDNS and 28.6% patients with SRNS were put off steroids. The number of patients was significantly greater in SDNS group as compared to patients with SRNS ($p<0.05$).

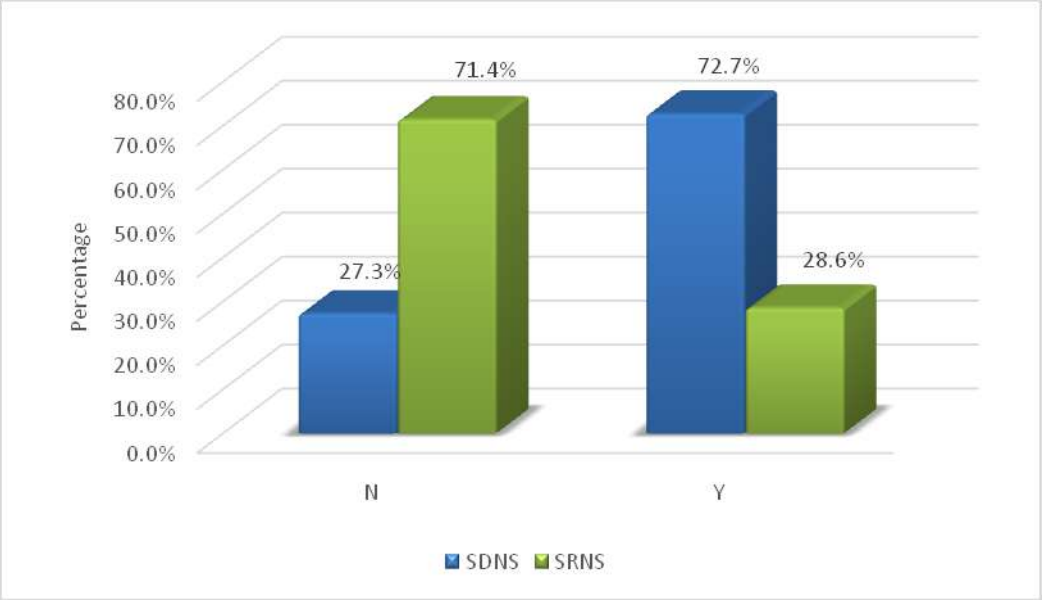


FIGURE NO.26: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON DISCONTINUATION OF STEROIDS

TABLE NO.27: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON TIME TAKEN AND DURATION OFF STEROID

	SDNS		SRNS		Z	p-value
	Median	IQR	Median	IQR		
Time taken to get off steroid post TAC	6.5	5-8.75	10.5	4-12	-1.228	0.219
Duration Off Steroids	5.50	3.25-7	1.50	0-8	-1.228	0.219
Steroid Dependent Dose	0.6	0.45-0.92	0.8	0.47-1	-1.062	0.288

The median duration taken to get off steroids post tacrolimus was 6.5 and 10.5 months in patients with SDNS and SRNS respectively. Upon statistical analysis, this was not found to be significant ($p>0.05$).

The median duration off steroids was 5.5 and 1.5 months in patients with SDNS and SRNS respectively. Upon statistical analysis, this was not found to be significant ($p>0.05$).

The median steroid dependent dose in patients who were not taken off steroids was 0.6 and 0.8 mg/kg/day in patients with SDNS and SRNS respectively. Upon statistical analysis, this was not found to be significant ($p>0.05$).

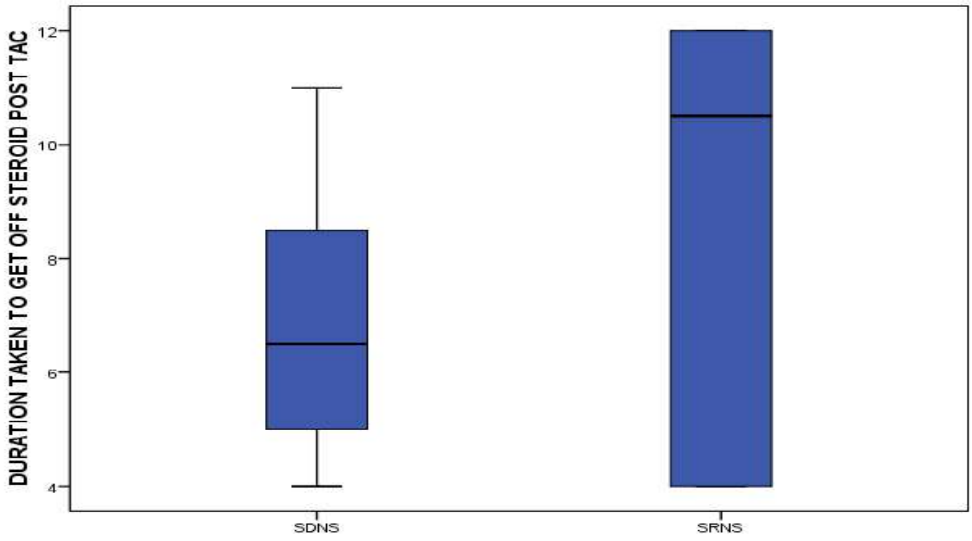


FIGURE NO.27A: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON TIME TAKEN TO GET OFF STEROID POST TAC.

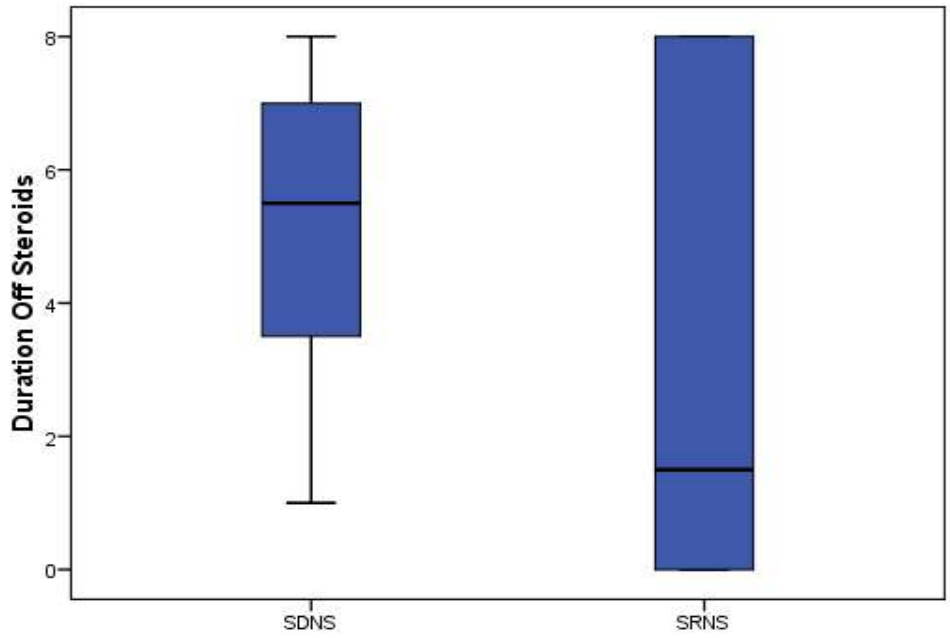


FIGURE NO.27B: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON DURATION OFF STEROID

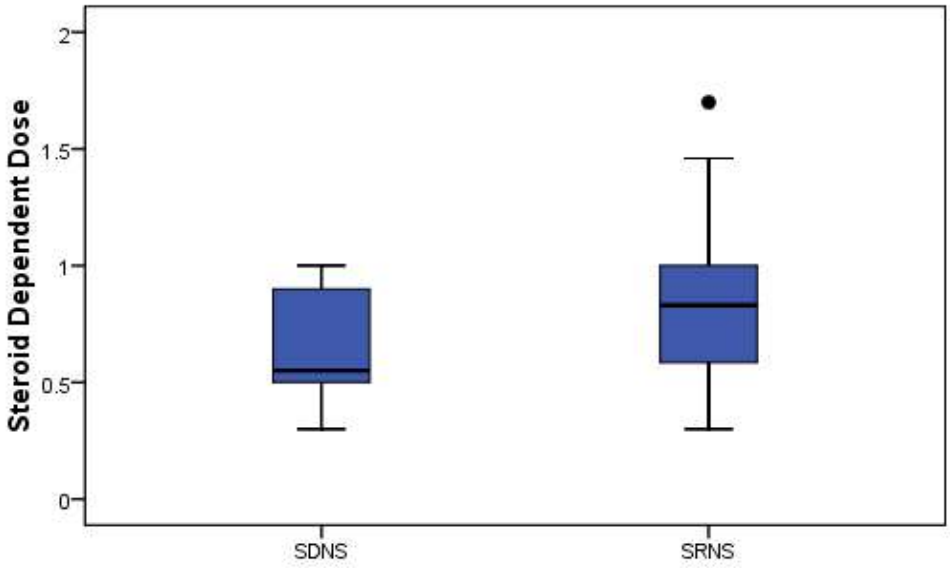


FIGURE NO.27C: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON STEROID DEPENDANT DOSE (POST TAC)

TABLE NO.28: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON PARTICIPANTS OFF STEROID ≥6 MONTHS

	SDNS		SRNS		Total		Chi-square value	p-value
	No. of cases	%age	No. of cases	%age	No. of cases	%age		
Off ≥ 6 month	8	36.4%	2	9.5%	10	23.3%	1.201	0.273

8 patients of SDNS and 2 patients of SRNS were put off steroids for≥ 6 months

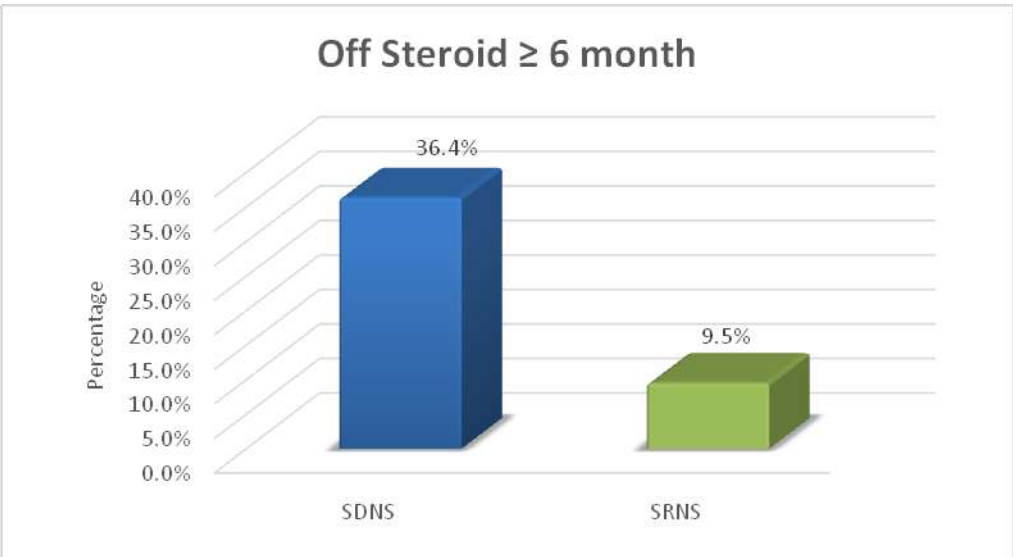


FIGURE NO.28: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON PARTICIPANTS OFF STEROID ≥ 6 MONTHS

TABLE NO.29: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON FIRST RELAPSE (MONTHS AFTER STARTING TACROLIMUS)

	SDNS		SRNS		Z	p-value
First Relapse (after starting Tacrolimus)	Median	IQR	Median	IQR		
Months	3.0	2-8.25	3.5	2-6.25	-0.056	0.955

The median time of first relapse after starting tacrolimus was 3 and 3.5 months in patients with SDNS and SRNS respectively. Upon statistical analysis, this was not found to be significant (p>0.05).

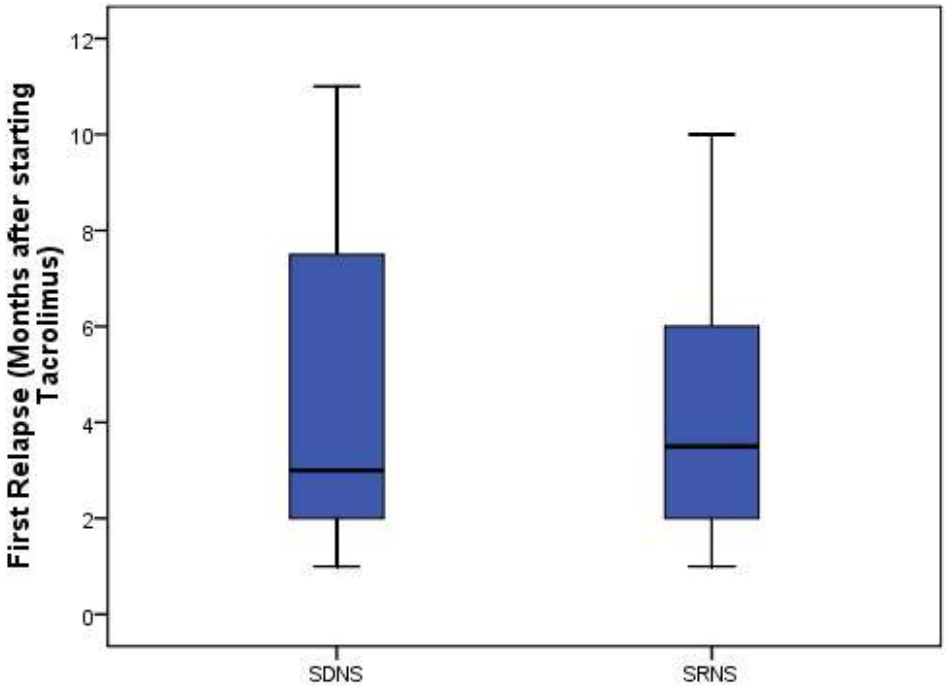


FIGURE NO.29: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON FIRST RELAPSE (MONTHS AFTER STARTING TACROLIMUS)

TABLE NO.30: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON NO. OF RELAPSES AFTER STARTING TACROLIMUS (IN 12 MONTHS PERIOD)

		SDNS		SRNS		Total		Chi-square value	p-value
		No. of cases	%age	No. of cases	%age	No. of cases	%age		
No. Of Relapses After Starting Tacrolimus (In 12 Months Period)	1	1	12.5%	8	44.4%	9	34.6%	5.631	0.228
	2	3	37.5%	3	16.7%	6	23.1%		
	3	1	12.5%	3	16.7%	4	15.4%		
	4	3	37.5%	4	22.2%	7	26.9%		
Total		8	100.0%	18	100.0%	26	100.0%		

	SDNS		SRNS		Z	p-value
No. Of Relapses After Starting Tacrolimus In 12 Months Period	Median	IQR	Median	IQR		
	0	0-2	2.0	1-3.25	-1.033	0.003

The median number of relapses after starting tacrolimus (in 12 months period) was 0 and 2 in patients with SDNS and SRNS respectively. Upon statistical analysis, this was found to be significant ($p<0.05$).

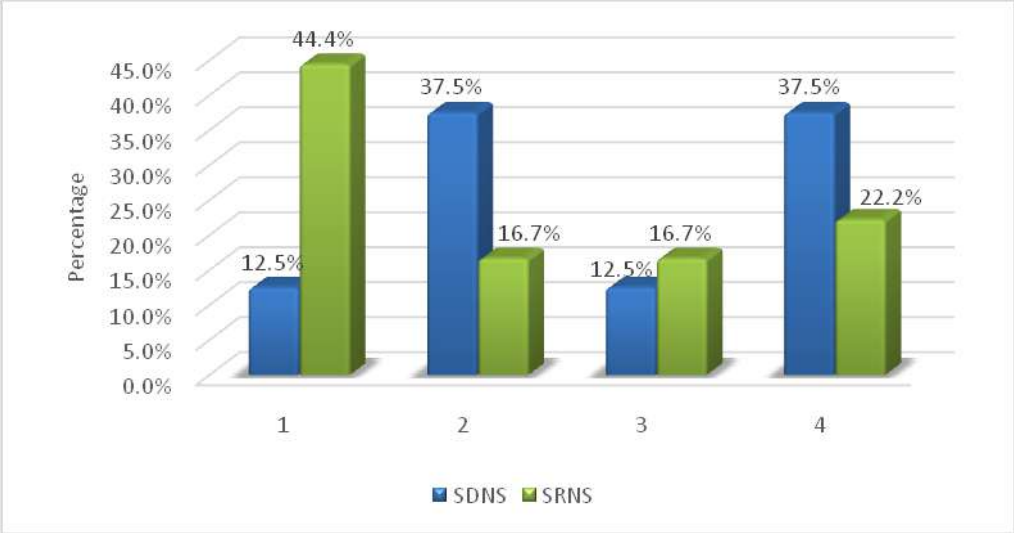


FIGURE NO.30A: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON NO. OF RELAPSES AFTER STARTING TACROLIMUS (IN 12 MONTHS PEROID)

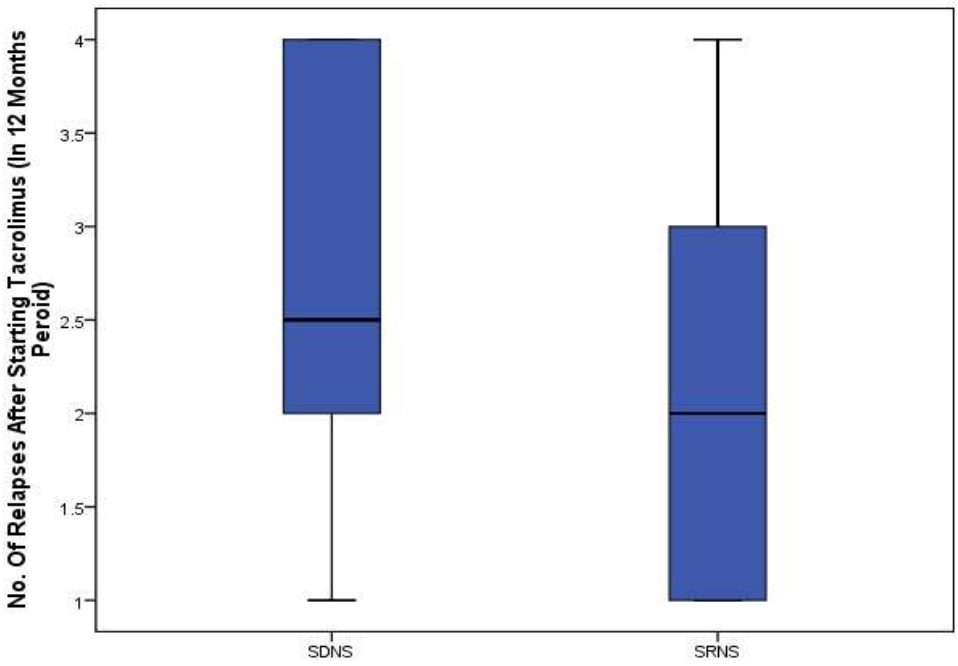


FIGURE NO.30B: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON NO. OF RELAPSES AFTER STARTING TACROLIMUS (IN 12 MONTHS PEROID)

TABLE NO.31: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON WEIGHT

	SDNS		SRNS		Z	p-value
Weight z score	Mean	SD	Mean	SD		
At Start	-0.2	1.4	-0.7	1.1	-1.227	0.220
After 1yr	-0.6	1.3	-1.0	1.4	-0.960	0.337
Difference	-0.42	0.87	-0.29	0.99		
p-value	0.046		0.118			

The mean weight z score of patients with SDNS at start of treatment with tacrolimus and at the end of 1 year was found to be -0.2 and -0.6 and SD (±1.4 and ±1.3) respectively. The difference z score was found to be -0.42. The weight was found to be significantly greater in patients with SDNS as compared to SRNS ($p<0.05$).

The mean weight z score of patients with SRNS at start of treatment with tacrolimus and at the end of 1 year was found to be -0.7 and -1.0 and SD (±1.1 and ±1.4) respectively. The difference z score was found to be -0.29.

FIGURE NO.31: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON WEIGHT

TABLE NO32: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON HEIGHT

	SDNS		SRNS		Z	p-value
	Mean	SD	Mean	SD		
Height z score	-1.2	1.2	-1.5	1.4	-1.130	0.258
HEIGHT z score after 1yr	-0.8	1.3	-1.1	1.3	-1.130	0.258
Diff Height z score	0.46	0.71	0.39	1.44		
p-value	0.013		0.375			

The meanheight z score of patients with SDNS at start of treatment with tacrolimus and at the end of 1 year was found to be -1.2 and -0.8 and SD (±1.2 and 1.3) respectively. The difference z score was found to be -0.46 SD ±0.71. The weight was found to be significantly greater in patients with SDNS as compared to SRNS ($p<0.05$).

The meanheight z score of patients with SRNS at start of treatment with tacrolimus and at the end of 1 year was found to be -1.5 and -1.1 and SD (±1.4 and 1.3) respectively. The difference z score was found to be 0.39.

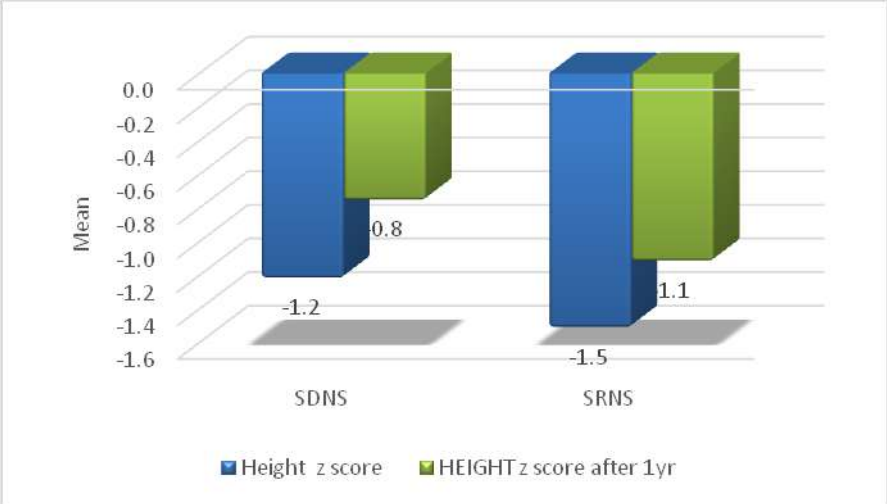


FIGURE NO32: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON HEIGHT

TABLE NO. 33: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON BMI

	SDNS		SRNS		Z	p-value
BMI z score	Mean	SD	Mean	SD		
At Start	2.4	4.4	0.2	1.8	-2.043	0.041
At 1 year	-0.1	1.3	-0.5	1.6	-0.782	0.434
Diff BMI Z	-2.53	4.40	-0.71	1.39		
p-value	0.001		0.070			

The mean BMI z score of patients with SDNS at start of treatment with tacrolimus and at the end of 1 year was found to be 2.4 and -0.1 and SD (±4.4 and ±1.3.) respectively. The difference z score was found to be -2.53 SD ±4.4. The weight was found to be significantly greater in patients with SDNS as compared to SRNS ($p<0.05$).

The mean BMI z score of patients with SRNS at start of treatment with tacrolimus and at the end of 1 year was found to be 0.2 and -0.5 and SD (±1.8 and ±1.6) respectively. The difference z score was found to be -0.71. SD ±1.39.

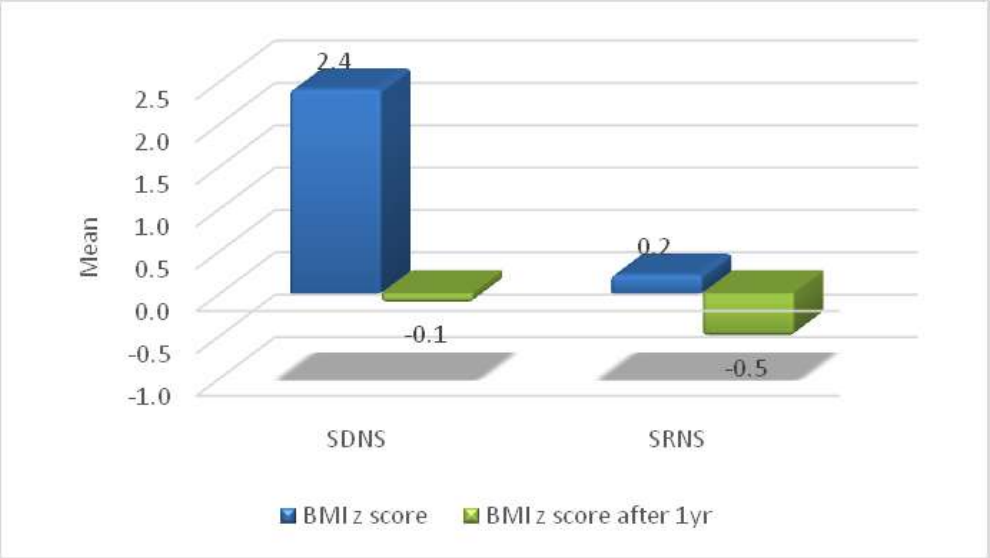


FIGURE NO.33: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON BMI

TABLE NO.34: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON OBESITY AT START AND AT 1 YEAR OF TACROLIMUS.

		SDNS		**SRNS**		Total		Chi-square value	p-value
Obesity		No. of cases	%age	No. of cases	%age	No. of cases	%age		
At Start	N	15	68.2%	16	76.2%	31	72.1%	0.343	0.558
	Y	7	31.8%	5	23.8%	12	27.9%		
At 1yr	N	20	90.9%	18	85.7%	38	88.4%	0.282	0.595
	Y	2	9.1%	3	14.3%	5	11.6%		
p-value		0.125		0.727					

Obesity was seen in 31.8% patients with SDNS and 23.8% patients with SRNS at start of treatment with Tacrolimus. It was observed that the total number of obese cases reduced after one year with 9.1% patients with SDNS and 14.3% patients with SRNS. Upon statistical analysis, this was not found to be significant (p>0.05).

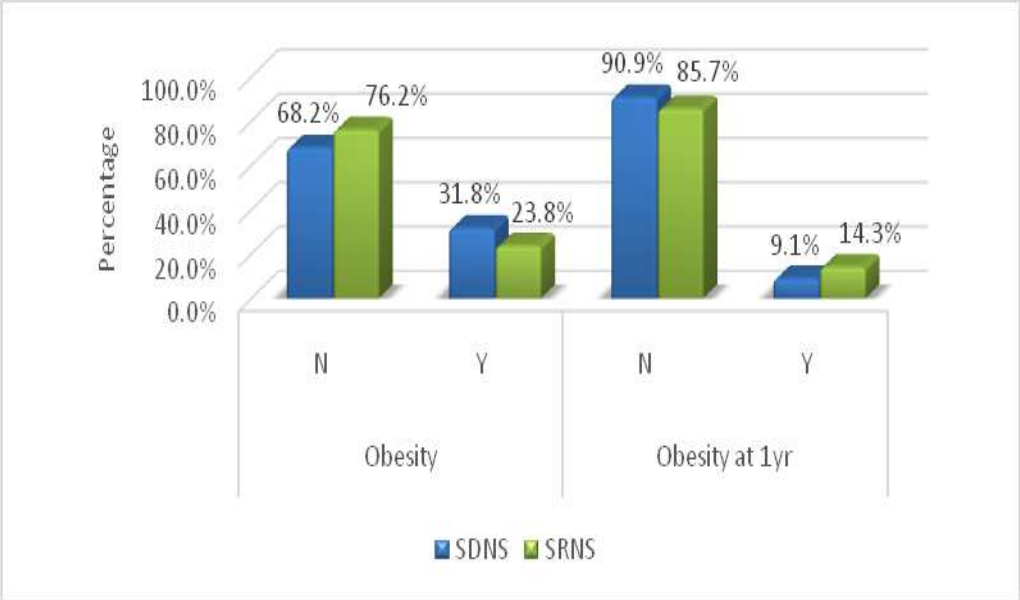


FIGURE NO.34: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON OBESITY AT START AND AT 1 YEAR OF TACROLIMUS.

TABLE NO.35: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON SHORT STATURE AT START AND AT 1 YEAR OF TACROLIMUS.

		SDNS		SRNS		Total		Chi-square value	p-value
Short Stature		No. of cases	%age	No. of cases	%age	No. of cases	%age		
At Start	N	17	77.3%	17	81.0%	34	79.1%	0.088	0.767
	Y	5	22.7%	4	19.0%	9	20.9%		
At 1year	N	19	86.4%	19	90.5%	38	88.4%	0.177	0.674
	Y	3	13.6%	2	9.5%	5	11.6%		
p-value		0.625		0.687					
Total		22	100.0%	21	100.0%	43	100.0%		

Short stature was seen in 22.7% patients with SDNS and 19% patients with SRNS at start of treatment with Tacrolimus. It was observed that the total number of cases reduced after one year with 13.6% in patients with SDNS and 9.5% in patients with SRNS. Upon statistical analysis, this was not found to be significant (p>0.05).

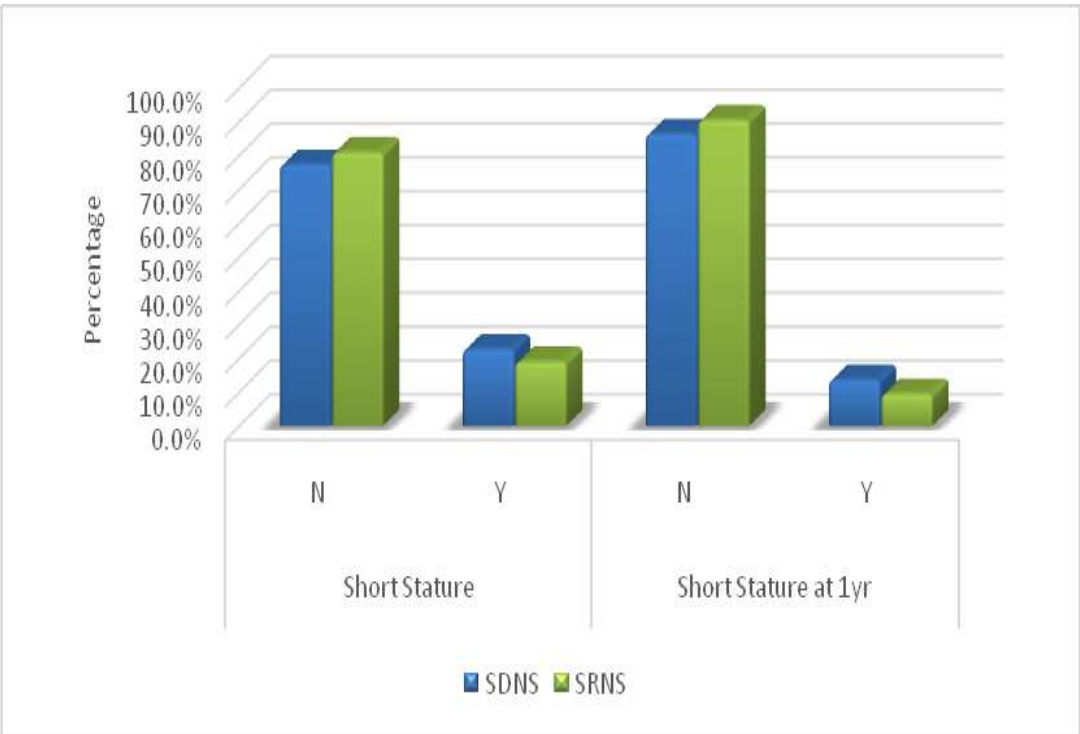


FIGURE NO.35: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON SHORT STATURE AT START AND AT 1 YEAR OF TACROLIMUS.

TABLE NO.36: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON TREATMENT FAILURE

		SDNS		**SRNS**		Total		Chi-square value	p-value
		No. of cases	%age	No. of cases	%age	No. of cases	%age		
Treatment Failure (Y/N)	N	18	81.8%	14	66.7%	32	74.4%	1.296	0.255
	Y	4	18.2%	7	33.3%	11	25.6%		

18.2% patients with SDNS and 25.6% patients with SRNS showed treatment failure. Upon statistical analysis, this was not found to be significant (p>0.05).

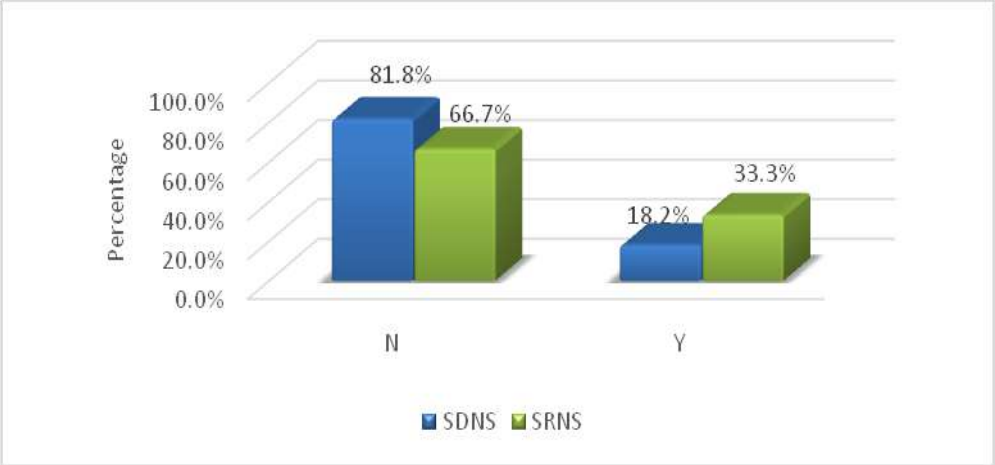


FIGURE NO.36: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON TREATMENT FAILURE

TABLE NO.37: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON CAUSE OF TREATMENT FAILURE & RELAPSES

		SDNS		SRNS		Total		Chi-square value	p-value
CAUSE OF TREATMENT FAILURE.		No. of cases	%age	No. of cases	%age	No. of cases	%age		
≥ 3 RELAPSES	Y	4	18.2%	7	33.3%	11	25.6%	5.835	0.04
Recurrence of SR (no response after relapse, after 4 weeks full dose steroids)	Y	0	0.0%	5	23.8%	5	11.6%	1.708	0.19
Irreversible increase in Sr Creatinine (< 50 ml/min/ 1.73m2)	N	0	0.0%	0	0.0%	0	0.0%		

Frequent relapse was found to be the cause of treatment failure in 18.2% patients with SDNS compared to 33.3% patients with SRNS. Upon statistical analysis, this was found to be significant ($p<0.05$).

Recurrence of SR was not seen in patients with SDNS and 23.8% patients with SRNS. Upon statistical analysis, this was not found to be significant ($p>0.05$).

None of the study participants had irreversible increase in serum creatinine.

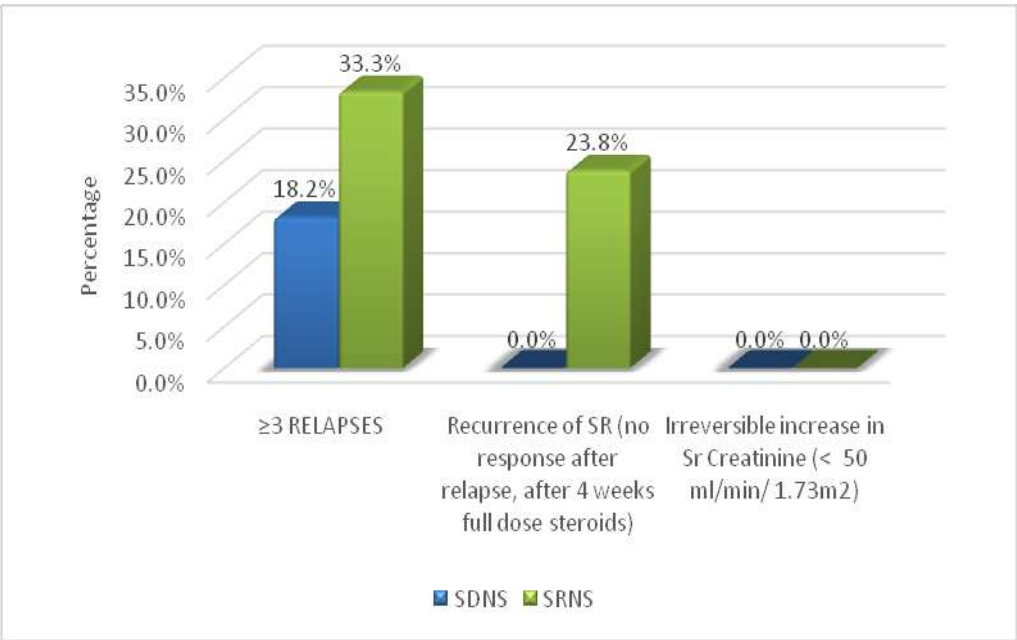


FIGURE NO.37: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON CAUSE OF TREATMENT FAILURE & RELAPSES

TABLE NO. 38: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON DISCONTINUATION OF TACROLIMUS

		SDNS		SRNS		Total		Chi-square value	p-value
		No. of cases	%age	No. of cases	%age	No. of cases	%age		
Tacrolimus Stopped (Y/N)	N	19	86.4%	21	100.0%	40	93.0%	3.078	0.233
	Y	3	13.6%	0	0.0%	3	7.0%		
Reason Of Stopping	FREQUENT RELAPSER	1	4.5%	0	0.0%	1	2.3%	3.078	0.380
	OFF TREATMENT	1	4.5%	0	0.0%	1	2.3%		
	POOR RESPONSE	1	4.5%	0	0.0%	1	2.3%		

Tacrolimus was stopped in 13.6% patients with SDNS and none of the patients with SRNS. In SDNS group, 3 patients were taken off Tacrolimus. Frequent relapse, Off treatment with Tac and poor response were the reason to stop tacrolimus. Upon statistical analysis, this was not found to be significant (p>0.05).

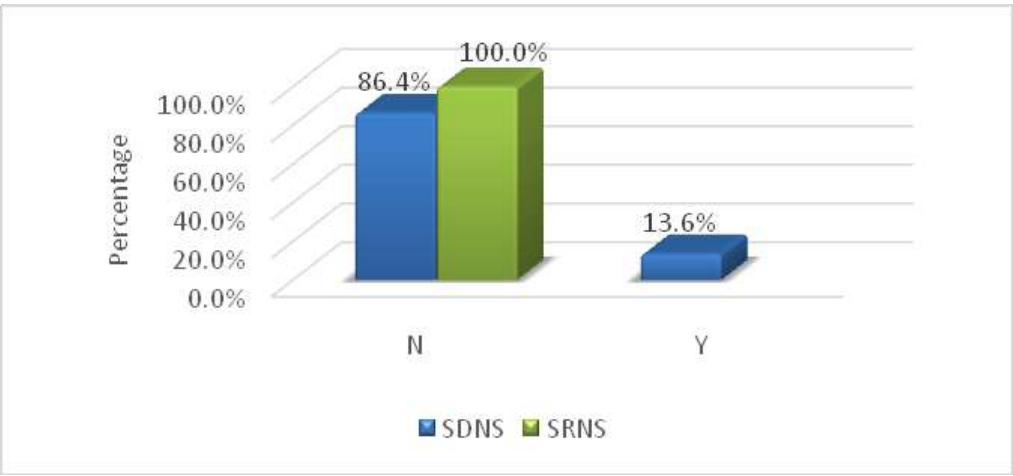


FIGURE NO. 38 A: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON DISCONTINUATION OF TACROLIMUS

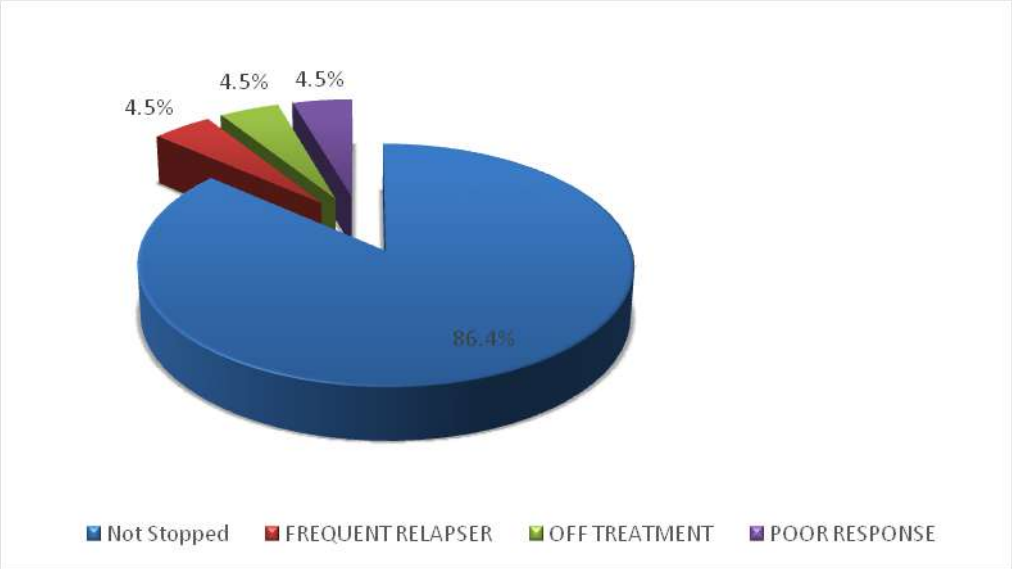


FIGURE NO. 38B: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON CAUSE OF DISCONTINUATION OF TACROLIMUS IN SDNS

TABLE NO.39: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON SUBSEQUENT TREATMENT (RITUXIMAB)

		SDNS		**SRNS**		Total		Chi-square value	p-value
		No. of cases	%age	No. of cases	%age	No. of cases	%age		
Drug Started (Rituximab) (Y/N)	N	20	90.9%	20	95.2%	40	93.0%	0.310	0.578
	Y	2	9.1%	1	4.8%	3	7.0%		
Total		22	100.0%	21	100.0%	43	100.0%		

Rituximab was started in 9.1% patients with SDNS and 4.8% patients with SRNS. Upon statistical analysis, this was not found to be significant (p>0.05).

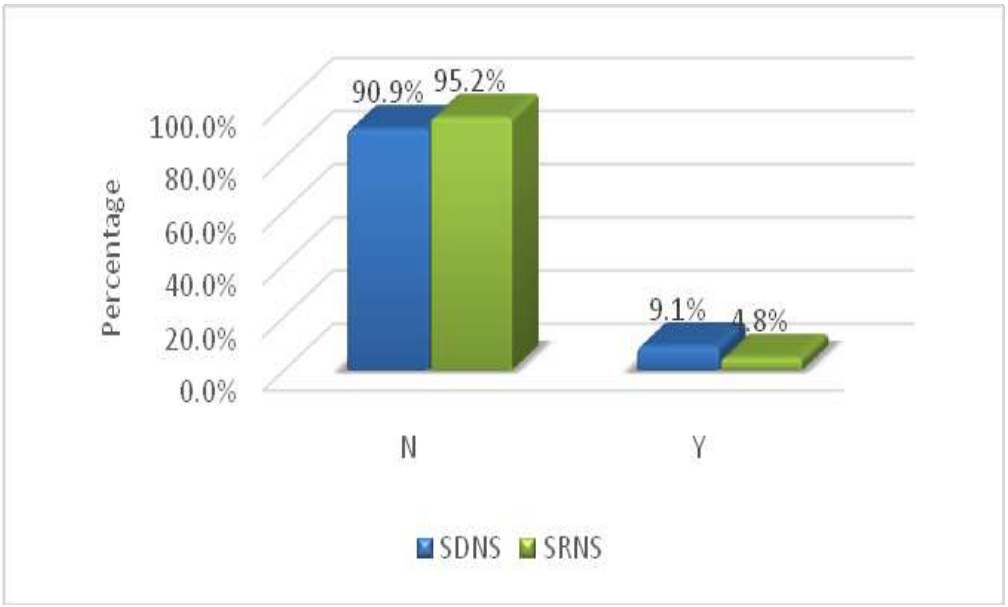


FIGURE NO.39: DISTRIBUTION OF STUDY PARTICIPANTS BASED ON SUBSEQUENT TREATMENT (RITUXIMAB)

DISCUSSION

The study “Efficacy of tacrolimus in steroid dependant and steroid resistant nephrotic syndrome” was a hospital based observational study, including 43 patients of steroid dependent nephrotic syndrome (SDNS) and steroid resistant nephrotic syndrome (SRNS). Children between the age group of 3 months to 18 years were included and tacrolimus was administered. We followed up patients who were already enrolled as well as new patient registered in paediatric Nephrology clinic for a minimum of 1 year in the Department of paediatrics of Dayanand Medical College and Hospital, Ludhiana Punjab.

Tacrolimus in Steroid dependent nephrotic syndrome

In our observational study on children with SDNS and SRNS, we looked at the efficacy of tacrolimus in inducing complete and partial remission. In our study, after 6 months of tacrolimus treatment, we observed complete remission in 19 children (86.4%), partial remission in 2 children (9.1%) and no remission in 1 child (4.5%)of SDNS group (n=22).At 12 months, complete remission, partial remission and no remission was seen in 90.9%, 4.5% and 4.5% patients with SDNS respectively.

Wang et al evaluated MMF and TAC in children with steroid sensitive but frequently relapsing or SDNS. In their study 38 were recruited to the TAC group and after 6 months In the TAC group there were 32 patients (84.2%) in complete remission and 4 patients (10.5%) achieving partial remission. Two patients (5%) had no remission at the end of 6 months of TAC. After 12 months 31 (84.2%), 3 (7.8%) and 3 (7.8%) patients were incomplete remission, partial remission and no remission respectively.[58] Our study had similar results. A retrospective study done by Saratlal et al to determine the efficacy of tacrolimus in steroid dependent and steroid resistant nephrotic syndrome with 19 and 21 patients respectively showed complete remission in 9 patients (47.36%), partial remission in five patients (26%) and no remission in

five patients (26%). Patients in complete, partial and no remission after 12 months of tacrolimus were 11 (57.9%), 5 (26%) and 4 (21%) respectively.[33] Westoff et al conducted an open, monocentric, non-randomized, prospective trial. Within 6 months, complete remission was achieved in 5 patients (50%) and partial remission in 4 patients (40%), yielding a final response rate of 90%,[27] similar to our study.

TAC in SRNS

In SRNS group, we had complete remission in 9 children (42.9%), partial remission in 3 children (14.3%) and no remission in 9 children (42.9%) (n=21) after 6 months of treatment with tacrolimus. Remission (CR+PR) was seen in 12 children (57.1%) Complete remission, partial remission and no remission was seen in 12 (57.1%), 3 (14.3%) and 6 (28.6%) patients with SRNS respectively at 12 months. Remission (CR+PR) was seen in 15 children (71.4%). In a randomized control trial done by Choudhry et al comparing tacrolimus and cylcosporin in SRNS patients with 21 patients, showed remission in 85.7% in tacrolimus group and 80% in cyclosporine group after 6 months& 90.5% and 85% in tacrolimus and cyclosporin group respectively at 12 month of treatment. They concluded that tacrolimus is similar in efficacy to cyclosporine and is associated with less adverse effects.[50] According to a retrospective study done by Saratlal et al to determine the efficacy of tacrolimus in steroid dependent and steroid resistant nephrotic syndrome with 19 and 21 patient respectively, remission (CR+PR) in16 (80.95%) children of SRNS group was observed[33]which is similar to our result. In a RCT trial done by Sinha at al where they examined the effect of switching from therapy with tacrolimus to MMF on disease course in an open label 1 to 1 randomised controlled trial in recently diagnosed children with SRNS (n=31) reported children receiving Tacrolimus throughout 12 month period had remission (CR+PR) in 11 children (35.4%).[60] Segarra A et al analysed the efficacy and safety of a combined therapy of tacrolimus and steroids in 25 patients with idiopathic primary focal

glomerulosclerosis and proven resistance to or dependence on cyclosporin A. After 6 months trial of tacrolimus and steroids, proteinuria decreased in 17 patients (68%), complete remission in 10 patients (40%), partial remission in two patients (8%) and a moderate reduction in proteinuria was seen in five additional patients (20%). After tacrolimus discontinuation, (76%) relapsed and were treated with a second trial of tacrolimus for 1 year, achieving complete remission in five patients (38.4%), partial remission in four patients (30.7%) and reduction of proteinuria in four patients (30.7%).[26]A study conducted by Kim J et al A retrospective chart review of pediatric subjects with idiopathic nephrotic syndrome was conducted at a single tertiary care center (2007–2012). Drug responses were classified as complete response, partial response, and no response. Of the 188 charts reviewed, 121 children were classified as SSNS and 67 children as SRNS; 58% were classified as FR-SSNS. Sixty-five subjects were diagnosed with focal segmental glomerulosclerosis via biopsy. Follow-up ranged from 6 months to 21 years. The combined rate of complete and partial response for mycophenolate mofetil (MMF) was 65% (33/51) in SSNS and 67% (6/9) in SRNS. For tacrolimus, the response rate was 96% (22/23) for SSNS and 77% (17/22) for SRNS. Eighty-three percent (5/6) of SSNS subjects treated with rituximab went into complete remission; 60% relapsed after B-cell repletion. Eight refractory subjects were treated with combined MMF/tacrolimus/corticosteroid therapy with a 75% response rate.[42] The remission in SDNS and SRNS were comparable to our study.

Steroid dependent dose in SDNS

In our study, the median steroid dependent dose at the start of treatment and at 12 months of treatment was 1.4 (1.23-1.5) and 0.55 (0.45-0.93) which was statistically significant. A study on efficacy of Rituximab vs Tacrolimus in Pediatric Corticosteroid-Dependent Nephrotic Syndrome, a randomized clinical trial with 60 patients in TAC group by Basu et al reported a significant decrease in prednisolone

dose (mg/kg/day) at 12 months (1.3).[55] In comparison with our study, we had significantly lower dependent dose after 12 months of treatment.

A retrospective study by Sinha et al comparing the short-term efficacy of rituximab versus tacrolimus observed decrease in cumulative steroid dose before (125.7±58.2) and after treatment with TAC (70.9±26.3).[57] Another study by J Wang et al had decreased steroid dose after treatment in TAC group after 1 year of treatment.[58]

Incidence relapse rate in SDNS

In our study incidence relapse rate seen in SDNS before and after tacrolimus in 12 months was 2.4 and 1 Relapse-Person-Year respectively. The difference of incidence relapse rate was (-1.4). Study done by J Wang et al study on evaluation of mycophenolate mofetil or tacrolimus in children with steroid sensitive but frequently relapsing or steroid-dependent nephrotic syndrome with 38 patients in SDNS/SS but frequently relapsing NS also found reduction in relapse rate from 2.39 to 0.41[58] which was coherent with our study. A retrospective study by Sinha et al comparing the short-term efficacy of rituximab versus tacrolimus in steroid-dependent nephrotic syndrome with 13 patients in tacrolimus group had similar findings of significant decline in number of relapses before and after treatment with TAC in SDNS. 8 patients of SDNS and 2 patients of SRNS were put off steroids for ≥ 6 months. [57]

Discontinuation of steroid

At the end of 12 months, our study observed significant proportion of children (n=22, 51.2%) were withdrawn from daily or alternate day prednisolone therapy. In SDNS group 16 children (72.7%) and 6 children (28.6%) in SRNS group were discontinued on prednisolone. Study done by Basu et al had similar result of 46 out of 58 children (79.3%) who were discontinued on steroid at 12 months with treatment of tacrolimus.[55]

First relapse

The median time of first relapse after starting tacrolimus was 3 (~13 weeks) and 3.5 (~15 weeks) months in patients with SDNS and SRNS respectively which was statiscally not significant. In a study done by Basu et al on efficacy of Rituximab vs. Tacrolimus in Pediatric Corticosteroid-Dependent Nephrotic Syndrome, a randomized clinical trial with 60 patients in TAC group reported SDNS patients receiving TAC had a median relapse of 29 weeks,[55] which was better in comparison to our study. A retrospective study by Sinha et al comparing the short-term efficacy of rituximab versus tacrolimus in steroid-dependent nephrotic syndrome with 13 patients in tacrolimus group reported the time to first relapse in patients given rituximab (8.5±5.1 months) was shorter than in those receiving tacrolimus (9.8±5.6 months); this difference was not significant (mean difference 1.3±2.8; 95% CI–4.7, 7.3; P=0.65). [57] In another study done by Choudhary et al in SRNS patients comparing efficacy and safety in tacrolimus vs. CsA had first relapse in 8.5 months range (7.3 to 10). [50]

Number of relapses

The median number of relapses after starting tacrolimus (in 12 months period) was 2.5 and 2 in patients with SDNS and SRNS respectively. In SDNS group 12 patients (57%) had no relapse and in SRNS group 3 patients did not have any relapse during 12 months of tacrolimus. Patients having 1 relapse during 1 year period of tacrolimus were 1 (12.5%) and 8 (44.4%) in SDNS and SRNS respectively. Patients having 2 relapses were 3 (37.5% and 16.7%) in both groups. Patients having 3 relapses were 1 (12.5%) and 3 (16.7%) in SDNS and SRNS respectively. Four relapses were seen in 3 (37.5%) and 4 (22.2%) patients of SDNS and SRNS group. In a study done by Wang et al on evaluation of mycophenolate mofetil or tacrolimus in children with steroid sensitive but frequently relapsing or steroid-dependent nephrotic syndrome with 38 patients in SDNS/SS but frequently relapsing NS found no relapse in tacrolimus group (n=38) at 12 months

were seen in 20 patients (64.5%).[58]A total of 9 (29%), 2 (6.5%) and 0 patients had 1, 2 and ≥3 relapses in 12-month period. Another study done by Sinha et al, comparing efficacy of rituximab versus tacrolimus in SDNS children at the end of 12 months had no relapse in 6 (46%) out of 13 children in TAC group. 5 (38.4%) children had 1-2 relapses, and 2 (15%) children had ≥3 relapses. [57] Our study was coherent to their results.

Tacrolimus levels

In our study both groups were started on tacrolimus at a median dose of 0.1 mg/kg. Median tacrolimus levels done at 12 months were 4.7 and 4.2 in SDNS and SRNS group. Overall median tacrolimus during 12 months were 4.05 and 3.40 in SDNS and SRNS. We observed that patients with SRNS had lower tacrolimus levels compared to SDNS patients. This could be attributed to persisting proteinuria and a greater number of relapses that was seen in SRNS group. Wang et al's study on evaluation of mycophenolate mofetil or tacrolimus in children with steroid sensitive but frequently relapsing or steroid-dependent nephrotic syndrome with 38 patients in SDNS/SS but frequently relapsing NS found the mean TAC trough blood level was 6.46 ± 1.81 (range 3.14–9.80)[58]. A retrospective study by Sinha et al comparing the short-term efficacy of rituximab versus tacrolimus in steroid-dependent nephrotic syndrome with 13 patients in tacrolimus group had trough tacrolimus levels at 12 months between 4 and 7 ng/ml.[57]Delbet et al's study on Infrequent tacrolimus-induced nephrotoxicity in French patients with steroid-dependent nephrotic syndrome with 21 patient receiving tacrolimus reported trough level of 5 (3.5–5.5)ng/ml at 12 months.[64]Study on efficacy of Rituximab vs. Tacrolimus in Pediatric Corticosteroid-Dependent Nephrotic Syndrome, a randomized clinical trial with 60 patients in TAC group by Basu et al reported in the tacrolimus group, mean (SD) trough tacrolimus serum levels at day 14 were 6.0 (0.5) µg/L.[55]A retrospective study done by Saratlal et al to determine the efficacy of tacrolimus in steroid

dependent and steroid resistant nephrotic syndrome with 19 and 21 patients respectively reported average tacrolimus trough level was 4.88mcg/L (SDNS+SRNS).[33]A study done by Choudhary et al on Tacrolimus Versus CsA in SRNS with 21 patient in tacrolimus group aimed for trough levels of tacrolimus and CsA between 5and 8 ng/mL and 100 to 150 ng/mL, respectively, lower levels were accepted if the patients were in remission. The mean daily dose of tacrolimus ranged between 0.10 and 0.12 mg/kg, and the trough level at 2 weeks was 4.6 ng/mL.[50]In our study, trough levels of tacrolimus were in concordance to above studies done in SDNS and SRNS patients.

Clinical profile and side effects

Gender

In this study, the majority of the study population was male, with 81.8% males and 18.2% females in the SDNS group and 76.2% males and 23.8% females in the SRNS group. Wang et al study on evaluation of mycophenolate mofetil or tacrolimus in children with steroid sensitive but frequently relapsing or steroid-dependent nephrotic syndrome with 38 patients in SDNS/SS but frequently relapsing NS receiving tacrolimus had 25 male (65.78%) and 13 (35%)female.[58]Study by Sinha et al comparing the short-term efficacy of rituximab versus tacrolimus in steroid-dependent nephrotic syndrome with 13 patients in tacrolimus group observed 10 (76.9%) male and 3 females (23.7%).[57] Study on efficacy of Rituximab vs Tacrolimus in Pediatric Corticosteroid-Dependent Nephrotic Syndrome, A Randomized Clinical Trial with 60 patients in TAC group by Basu et al reported 53.3% males and 46.7% females.[55]

Study by Choudhary et al comparing efficacy and safety of Tacrolimus versus CsA in 21 patients of TAC and 20 patients of CsA group had 14 males (66.7%) and 8 females (33.3%)[50] similar to our study. Study by Sinha et al in MMF versus tacrolimus for steroid-resistant nephrotic

syndrome in 31 patients of TAC and 29 patients of MMF group had 23 males (74.2%) and 8 females (25.8%)[55] similar to our study.

Age of onset

In our study, the median age was 3.8 years for all participants, with a higher median age of 6.8 years for SDNS patients and 5 years for SRNS patients. The highest number of patients in both groups was between 6-10 years of age. Wang et al study on evaluation of mycophenolate mofetil or tacrolimus in children with steroid sensitive but frequently relapsing or steroid-dependent nephrotic syndrome with 38 patients in SDNS/SS but frequently relapsing NS receiving tacrolimus found mean age of onset was 4.24 ± 2.68 (years) [58]. Study by Sinha et al comparing the short-term efficacy of rituximab versus tacrolimus in steroid-dependent nephrotic syndrome with 13 patients in tacrolimus group had mean age of onset of NS 3.6±2.2 (years). [57] Delbet et al's study on Infrequent tacrolimus-induced nephrotoxicity in French patients with steroid-dependent nephrotic syndrome with 21 patient receiving tacrolimus reported 4 (2.6–5.5) (years) as mean age of onset of NS.[64]A study done by Choudhary et al on Tacrolimus Versus CsA in SRNS with 21 patient in tacrolimus group reported mean age at onset (years) was 4.92, [50] and another study done by A Sinha et al on MMF versus tacrolimus for steroid-resistant nephrotic syndrome with 31 patients in tacrolimus arm reported mean age at onset of NS (years) was 4.17(2 to 6.58).[55]

Steroid adverse effect

In our study, ***Cushingoid features*** were seen in 32.6% of study participants. 31.8% in SDNS group and 33.3% in SRNS group had cushingoid features. Study by Sinha et al comparing the short-term efficacy of rituximab versus tacrolimus in steroid-dependent nephrotic syndrome with 13 patients in tacrolimus group reported cushingoid features were reported in all patients before starting treatment with tacrolimus. A study done by Choudhary et al on Tacrolimus Versus

CsA in SRNS with 21 patient in tacrolimus group also reported cushingoid in 7 (33%) patients of SRNS, [50] which was comparable to our study.

Hypertension, in our study was more in patients with SRNS as compared to SDNS group 52.4% and 36.4% respectively. A total of 44.2% had hypertension secondary to use of steroid (Prednisolone). Wang et al study on evaluation of mycophenolate mofetil or tacrolimus in children with steroid sensitive but frequently relapsing or steroid-dependent nephrotic syndrome with 38 patients in SDNS/SS but frequently relapsing NS receiving tacrolimus found both at the beginning and at the end of the trial, there were no significant changes between the two groups. Although during the trial there were two new-onset hypertensions in the TAC group. [58] Study by Sinha et al comparing the short-term efficacy of rituximab versus tacrolimus in steroid-dependent nephrotic syndrome with 13 patients in tacrolimus group reported hypertension in 12 (92.3%) patients. [57] Another study done by A Sinha et al on MMF versus tacrolimus for steroid-resistant nephrotic syndrome with 31 patients in tacrolimus arm reported 12 (38.7%) having hypertension secondary to steroid use.[55]

Obesity was seen in 27.9% of study participants. 31.8% in SDNS group and 23.8% in SRNS group were obese. The mean weight z score of patients with SDNS at start of treatment with tacrolimus and at the end of 1 year was found to be -0.2 and -0.6 and SD (±1.4 and ±1.3) respectively. The difference z score was found to be -0.42. The weight was found to be significantly greater in patients with SDNS as compared to SRNS. The mean BMI z score of patients with SDNS at start of treatment with tacrolimus and at the end of 1 year was found to be 2.4 and -0.1 and SD (±4.4 and ±1.3.) respectively. The difference z score was found to be -2.53 SD ±4.4. The weight was found to be significantly greater in patients with SDNS as compared to SRNS ($p<0.05$).Study by Sinha et al comparing the short-term efficacy of rituximab versus tacrolimus in steroid-dependent nephrotic syndrome

with 13 patients in tacrolimus group reported obesity in 6 (46.5%) patients. They also observed reduction in mean BMI from 1.7±0.8 pretreatment to 1.5±0.9 after 1 year of treatment.[57]Study on efficacy of Rituximab vs. Tacrolimus (TAC) in Pediatric Corticosteroid-Dependent Nephrotic Syndrome, A Randomized Clinical Trial with 60 patients in TAC group by Basu et al reported obesity in 6 (10%) patient. BMI z score was 2.2 and 1.66 before and after treatment with TAC.[55]

Our study found mean weight z score of patients with SRNS at start of treatment with tacrolimus and at the end of 1 year was found to be -0.7 and -1.0 and SD (±1.1 and ±1.4) respectively. The difference z score was found to be -0.29.

The mean BMI z score of patients with SRNS at start of treatment with tacrolimus and at the end of 1 year was found to be 0.2 and -0.5 and SD (±1.8 and ±1.6) respectively. The difference z score was found to be -0.71. SD ±1.39. Study done by A Sinha et al on MMF versus tacrolimus for steroid-resistant nephrotic syndrome with 31 patients in tacrolimus arm reported baseline mean BMI of 0.94 (-0.51 to 1.81).[55]

Short Stature was seen in 22.7% and 13.6% of patients with SDNS at start and after one year of treatment with Tacrolimus. The mean height z score of patients with SDNS at start of treatment with tacrolimus and at the end of 1 year was found to be -1.2 and -0.8 and SD (±1.2 and 1.3) respectively. The difference z score was found to be -0.46 SD ±0.71. Study by Sinha et al comparing the short-term efficacy of rituximab versus tacrolimus in steroid-dependent nephrotic syndrome with 13 patients in tacrolimus group reported short stature in 8 (61.53%) patients. Mean height standard deviation (SDS) was -2.3±1.8 and -2.4±1.5 after treatment with tacrolimus.[57] Wang et al study on evaluation of mycophenolate mofetil or tacrolimus in children with steroid sensitive but frequently relapsing or steroid-dependent nephrotic syndrome with 38 patients in SDNS/SS but frequently relapsing NS receiving tacrolimus found mean height -0.85±0.15 and -0.79±0.21before and after treatment with tacrolimus.[58]

In our study, the mean height z score of patients with SRNS at start of treatment with tacrolimus and at the end of 1 year was found to be -1.5±1.4 and -1.1±1.3 respectively. A study done by Choudhry et al on Tacrolimus Versus CsA in SRNS with 21 patients in tacrolimus group reported baseline mean height SDS of 0.05 (-0.41 to 0.5).[50] Study done by A Sinha et al on MMF versus tacrolimus for steroid-resistant nephrotic syndrome with 31 patients in tacrolimus arm reported baseline mean height SDS of -1.66 (-2.9 to-0.76).[60]

Behavioral changes were noted in 4.5% (1 case) in SDNS group. The child was observed to have developed aggression and had short temper which was not present before starting steroids.

Tacrolimus induced adverse effects

Adverse effects in SDNS group of our study induced secondary to tacrolimus use was hypertension, being the most common side effect, occurring in 5 cases (22.7% of patients) after starting tacrolimus. Other side effects included Diarrhea, UTI, Reversible Nephropathy, Chicken Pox, Pyoderma, Pneumonia, and Bronchiolitis, each occurring in one case (4.5% of patients).

No cases of Hyperkalemia, Seizure, Increase Blood Sugar, Increase OT/ PT, Hypertrichosis, Gingival Hyperplasia, or Acne were reported in SDNS patients.

Wang et al study on evaluation of mycophenolate mofetil or tacrolimus in children with steroid sensitive but frequently relapsing or steroid-dependent nephrotic syndrome with 38 patients in SDNS/SS but frequently relapsing NS receiving tacrolimus reported two children were discontinued because of severe drug-related adverse effects (severe infection and neurologic symptoms), and one child withdrew from the study due to NR. Two patients had to discontinue therapy due to severe neurologic symptoms and refractory anemia. Most common were infection, which occurred in three (7.89%) of the TAC patients. Gastrointestinal symptoms were also relatively common; these

symptoms were observed in one patient in the TAC group. Acute kidney injury did not occur in any TAC patients. Leucopoenia occurred in one patient. There were transient increases in the transaminase levels that did not require a dose reduction in two patients in the TAC group. New-onset hypertension occurred in two TAC patients who were given antihypertensive therapy. No significant abnormalities observed in blood glucose level and glucose intolerance.[58]

Study by Sinha et al comparing the short-term efficacy of rituximab versus tacrolimus in steroid-dependent nephrotic syndrome with 13 patients in tacrolimus group reported one patient receiving tacrolimus had reversible nephrotoxicity. No serious infections were noted during the follow-up period. [57] Study on efficacy of Rituximab vs Tacrolimus in Pediatric Corticosteroid-Dependent Nephrotic Syndrome, A Randomized Clinical Trial with 60 patients in TAC group by Basu et al reported among dermatological adverse effects, only one patient experienced hirsutism, while no cases of allergic reactions or flushing were observed. In terms of pulmonary adverse effects, pneumonitis was observed in seven patients, with one patient experiencing wheezing. Infections were also observed, with six patients experiencing upper respiratory tract infections, four patients experiencing infectious diarrhea, five patients experiencing skin infections, and two patients experiencing urinary tract infections. Hematological side effects included anemia in two patients, lymphopenia in one patient, and neutropenia in two patients. Two patients experienced hypertension, while three patients experienced vomiting, four patients experienced gastritis, and two patients experienced stomatitis. Metabolic and laboratory effects included increased alkaline phosphatase in two patients, increased ALT/AST in one patient, increased CPK in one patient, and hyperglycemia in four patients. Neuro-psychiatric effects were rare, with only one patient experiencing cognitive disturbance and one patient experiencing mood alteration. In terms of severe adverse events, one patient experienced grade 3 pneumonitis, while two patients experienced grade 3

wheezing. One patient experienced herpes zoster infection, one patient experienced infectious diarrhea, and one patient experienced hyponatremia. One patient experienced grade 3 hypertension. However, no cases of grade 3 lymphopenia or esophageal candidiasis were observed. Overall, patients receiving tacrolimus treatment for SDNS should be closely monitored for these potential adverse effects.[55]

In our study, patients with steroid-resistant nephrotic syndrome (SRNS), adverse effects were observed in various body systems. Hypertension was reported in 13 cases, accounting for 61.9% of the patients. Other common adverse effects included diarrhea in 4 cases (19.0%), urinary tract infections in 3 cases (14.3%), and pneumonia in 2 cases (9.5%). Bronchiolitis and acute tonsillitis were also reported in 4.8% of the patients each. No cases of reversible nephropathy, chickenpox, pyoderma, hyperkalemia, seizure, increased blood sugar, and increase in OT/PT, hypertrichosis, gingival hyperplasia, or acne were observed in the patients.

Study done by Choudhry et al on Tacrolimus Versus CsA in SRNS with 21 patient in tacrolimus group reported HTN- at 12 months in 5(23.8%) patients, Persistent nephro toxicity in 1 (4.7%) patient, Reversible nephro toxicity in 7 (33.3%) patients, Worsening of hypertension in 2(9.5%) patients, Neurological- headache paraesthesia in one patient (4.7%) patient. In Cosmetic changes-Hypertrichosis in none, gingival hyperplasia in 1 (4.7%) patient, Acne skin infection in 2 (9.5%) patients, Diarrhea in 6 patients (28.28 %) and pneumonia in one patient (4.7%). [50]

Study done by A Sinha et al on MMF versus tacrolimus for steroid-resistant nephrotic syndrome with 31 patients in tacrolimus arm reported Among serious adverse events, 3% of patients experienced anasarca, hypovolemia, peritonitis, or corticosteroid-related behavior, while 9.7% of patients experienced severe pneumonia, diarrhea with dehydration, or dengue hemorrhagic fever with shock. The most

common were upper respiratory infections, with 26% of patients experiencing them, followed by abdominal pain (9%), vomiting (9%), and pyoderma or impetigo (9%). Fever was reported by 10% of patients, while diarrhea and headache were reported by 6% and 7% of patients, respectively. Seizures were reported by only one patient, while cataract and thrombocytosis were each reported by one patient as well. Some patients also experienced changes in their laboratory values, such as acute kidney injury (3%), raised transaminases (6%), anaemia (6%), leukopenia (1%), persistent thrombocytopenia (3%), and thrombocytosis (1%). [60]

Treatment failure

Four (18.2%) patients with SDNS had treatment failure and the cause of treatment failure was frequent relapses in all patients. No patient had recurrence of steroid resistance or irreversible increase in serum creatinine.

Study by Sinha et al comparing the short-term efficacy of rituximab versus tacrolimus in steroid-dependent nephrotic syndrome with 13 patients in tacrolimus group reported treatment failure in 2 (15.3%) patients cause being frequent relapses.[57]Study on efficacy of Rituximab vs Tacrolimus in Pediatric Corticosteroid-Dependent Nephrotic Syndrome, A Randomized Clinical Trial with 60 patients in TAC group. Basu et al reported treatment failure in 6 (10%) of patients. Frequent relapses were attributed to be the cause.[55] Another retrospective study done by Saratlal et al to determine the efficacy of tacrolimus in steroid dependent and steroid resistant nephrotic syndrome with 19 and 21 patients respectively had treatment failure in 4 (21.5%) patient caused by frequent relapses in SDNS group. In SRNS group 5 (23.8%) patients went into treatment failure at 12 months of treatment with TAC. Cause of treatment failure could be linked to frequent relapses.[33]

In our SRNS study group, 7 (25.6%) patients went into treatment failure, frequent relapse in all seven patients and recurrence of steroid resistance in 5 out of 7 patients being the cause. No patients in SRNS group showed irreversible rise in serum creatinine. A study done by Choudhary et al on Tacrolimus Versus CsA in SRNS with 21 patient in tacrolimus group reported treatment failure in patients on tacrolimus therapy (3 patients) included 1 each with persistent nephrotoxicity (at 8 weeks of therapy) and no response to tacrolimus.[50] Study done by A Sinha et al on MMF versus tacrolimus for steroid-resistant nephrotic syndrome with 31 patients in tacrolimus arm reported treatment failure in 3 (9.7%) patients, cause being frequent relapses. No patient in SRNS had developed steroid resistance.[60]

SUMMARY AND CONCLUSION

This study aimed to evaluate the effectiveness of tacrolimus in reducing relapse rates in children with nephrotic syndrome, as well as its safety profile. The study enrolled 43 patients, divided into SDNS and SRNS groups, with the SDNS group having an earlier onset of the disease than the SRNS group. The study found that tacrolimus was effective in reducing the number of relapses in both groups, with SDNS patients experiencing a greater reduction. The study also found that tacrolimus was generally safe, with some adverse effects, such as hypertension, observed in both groups. Overall, the study suggests that tacrolimus may be a useful treatment option for children with nephrotic syndrome who do not respond to conventional therapy.

- The study enrolled a total of 43 patients who met the inclusion criteria. The patients were divided into two groups: SDNS and SRNS. The SDNS group consisted of 22 patients, while the SRNS group consisted of 21 patients.
- The study participants of SDNS group had a median age of 6.8 years and the SRNS group had a median age of 5 years.
- The median age of onset of nephrotic syndrome was 5.5 years, with the SDNS group having an earlier onset at 3.5 years compared to the SRNS group at 4 years (p-value > 0.05).
- The study population had a higher proportion of males than females, with 81.8% males and 18.2% females in the SDNS group, and 76.2% males and 23.8% females in the SRNS group.
- The study found that 18.2% of patients with SDNS and 33.3% of patients with SRNS had hypertension at onset of Nephrotic Syndrome. Overall, 25.6% of the total study participants had hypertension at onset of nephrotic Syndrome (p-value > 0.05).
- The study observed that 18.2% of patients with SDNS and 4.8% of patients with SRNS had microscopic haematuria at onset of

NS. Overall, 11.6% of the total study participants had microscopic haematuria at onset of NS.

- Patients with SDNS had a median number of 3 (1-4) relapses in the last year before starting tacrolimus. After starting tacrolimus, the median number of relapses was 0 (0-2) which was statistically significant (p-value >0.05).
- Prior to starting tacrolimus, almost half (45.5%) of the patients with SDNS and 76.2% of patients with SRNS were only on steroids.
- Prior to starting tacrolimus, 36.4% of SDNS patients were on levamisole. Patients on cyclophosphamide were (36.4%) and mycophenolate were (40.9%). In SRNS, 23.8% patients were on cyclosporine, but this was not statistically significant.
- Before the start of tacrolimus, all patients with SDNS achieved complete remission, while only 4.8% of patients with SRNS achieved partial remission and 95.2% showed no remission. This difference was statistically significant ($p<0.05$).
- Median starting dose of tacrolimus in both groups was 0.1 mg/kg
- The median serum albumin levels at the start of treatment were higher in patients with SDNS (2.78) compared to SRNS (1.64). After 12 months of treatment, the median serum albumin levels improved in both groups, with SDNS patients having higher levels (3.44) compared to SRNS patients (2.90).
- The median tacrolimus levels of patients with SDNS and SRNS were found to be 4.05 and 3.4, respectively
- The median duration of tacrolimus treatment was longer in the SRNS group (25 months) compared to the SDNS group (15.5 months).
- In the study, hypertension was more prevalent in patients with SRNS compared to those with SDNS, with 61.9% of SRNS patients experiencing hypertension compared to 22.7% of SDNS patients. Chicken pox and pyoderma were only observed

in one patient in the SDNS group. Additionally, diarrhea, UTI, pneumonia, and bronchiolitis were observed in a small percentage of patients in both groups, with SRNS patients showing slightly higher prevalence rates for most of these side effects. Reversible nephrotoxicity was seen in one patient of SDNS which resolved spontaneously.

- At 6 months of treatment with tacrolimus, it was found that a higher percentage of patients with SDNS achieved complete remission (86.4%) compared to patients with SRNS (42.9%). The response rate (CR+PR) was also higher in patients with SDNS (95.5%) compared to patients with SRNS (57.2%). The difference in response status (CR+PR) between the two groups of patients was found to be statistically significant ($p<0.05$).
- Higher complete remission rates were observed at 12 months in SDNS patients (90.9%) compared to SRNS patients (57.1%). More patients with SDNS responded to TAC (95.4%) than those with SRNS (71.4%), with a statistically significant difference between the groups (p-value <0.05).
- In SDNS, the median dependent dose before and after treatment with TAC were 1.4 IQR (1.23-1.5) and 0.55 IQR (0.45-0.93) mg/kg/day, respectively. The difference between the dependent dose before and after one year of tacrolimus was -0.85 mg/kg, which was found to be statistically significant (p-value < 0.05).
- Incidence relapse rate seen in SDNS before and after tacrolimus in 12 month was 2.4 and 1 respectively. The difference of Incidence relapse rate was -1.4 which was significant.
- After treatment with tacrolimus, a greater percentage of patients with SDNS (72.7%) compared to patients with SRNS (28.6%) were taken off steroids, and the difference was statistically significant ($p<0.05$).

- The median time taken to stop steroids post-tacrolimus was 6.5 months for SDNS and 10.5 months for SRNS, (p-value > 0.05)
- The median duration of steroid cessation was 5.5 months for SDNS and 1.5 months for SRNS post tacrolimus administration for 12 months.
- After 12 months of tacrolimus administration, the median steroid-dependent dose for patients who were not taken off steroids was 0.6 mg/kg/day for SDNS and 0.8 mg/kg/day for SRNS.
- After 12 months of receiving tacrolimus, 8 patients with SDNS and 2 patients with SRNS were able to stop taking steroids for at least 6 months.
- After 12 months of tacrolimus treatment, the median time to the first relapse was 3 months for SDNS and 3.5 months for SRNS.
- The median number of relapses after starting tacrolimus (in 12 months period) was 2.5 and 2 in patients with SDNS and SRNS respectively.
- In patients with SDNS, the mean height z score at the start of tacrolimus treatment was -1.2 (SD ±1.2) and at the end of 1 year was -0.8 (SD ±1.3), with a difference of -0.46 (SD ±0.71). Patients with SDNS had significantly greater height compared to patients with SRNS ($p<0.05$). In patients with SRNS, the mean height z score at the start of tacrolimus treatment was -1.5 (SD ±1.4) and at the end of 1 year was -1.1 (SD ±1.3), with a difference of 0.39.
- In patients with SDNS, the mean BMI z score at the start of tacrolimus treatment was 2.4 (SD ±4.4) and at the end of 1 year was -0.1 (SD ±1.3), with a difference of -2.53 (SD ±4.4). Patients with SDNS had significantly greater BMI compared to patients with SRNS ($p<0.05$).
- 18.2% patients with SDNS and 25.6% patients with SRNS showed treatment failure.

- Frequent relapse was a significant cause of treatment failure in 18.2% of patients with SDNS compared to 33.3% of patients with SRNS ($p<0.05$). Recurrence of steroid resistance was not observed in patients with SDNS, while it was observed in 23.8% of patients with SRNS.

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Sr. No.	Name	Age (YEARS)	Sex	Date of birth	Age Of Onset (Year / Month)	Urban/ Rural	File No. (Ped. Nephro)	Diagnosis (FRNS/SDNS/ SRNS)	Group	Hypertension at onset (Y/N)	Microscopic Haematuria at onset (Y/N)	Dependent Dose (Mg/Kg/Day) (If SDNS)	No Of Relapse Last One Year (Before Tacrolimus)	Prior Immunosuppressives	Levamisole (Y/N)	Cyclophosphamide (Y/N)	Mycophenolate (Y/N)
1	SN	4.0	M	15-01-2018	4.0	U	610	SDNS	1	Y	Y	1.3	0	N	N	N	N
2	AS	7.0	M	16-09-2014	5.0	U	581	SDNS	1	N	N	1.5	2	N	N	N	N
3	AS	8.0	M	11-05-2013	6.0	U	580	SDNS	1	N	N	1.2	3	N	N	N	N
4	GS	4.0	M	03-01-2017	4.0	R	571	SDNS	1	N	N	1.5	0	N	N	N	N
5	E	5.0	M	29-12-2015	3.8	R	577	SDNS	1	N	N	1.5	0	Y	N	N	Y
6	ES	5.0	M	11-04-2016	2.5	R	562	SDNS	1	N	N	1.5	4	N	N	N	N
7	GK	3.0	M	01-04-2019	1.4	U	537	SDNS	1	N	N	1	3	N	N	N	N
8	DJ	12.8	F	28-10-2008	9.0	U	536	SDNS	1	N	N	1	0	N	N	N	N
9	R	1.6	M	06-11-2018	1.6	U	520	SDNS	1	N	N	1	1	N	N	N	N
10	KP	6.5	M	27-03-2014	3.5	R	480	SDNS	1	N	N	1.3	3	Y	Y	Y	Y
11	OS	11.0	M	10-06-2008	10.0	U	437	SDNS	1	N	N	1.2	4	Y	N	N	Y
12	H	4.0	F	30-12-2012	3.5	U	362	SDNS	1	N	Y	1.5	3	Y	Y	N	N
13	GK	7.0	F	20-04-2009	6.0	R	336	SDNS	1	N	N	1	3	Y	N	Y	N
14	M	2.0	M	11-04-2014	1.5	R	305	SDNS	1	Y	N	1.4	2	N	N	N	N
15	H	9.0	M	24-09-2010	3.0	U	310	SDNS	1	N	N	1.5	4	Y	Y	Y	Y
16	G	5.0	F	23-04-2010	4.0	U	269	SDNS	1	Y	N	0.6	2	Y	N	N	Y
17	S	9.4	M	26-05-2012	1.9	U	239	SDNS	1	N	N	1.5	2	Y	Y	Y	N
18	S	5.5	M	28-03-2010	2.0	U	134	SDNS	1	N	N	0.32	4	Y	Y	Y	Y
19	JS	17.0	M	28-01-2005	5.0	U	99	SDNS	1	Y	N	1.3	4	Y	Y	Y	Y
20	IS	13.0	M	29-11-2007	0.8	U	26	SDNS	1	N	Y	0.85	4	Y	Y	Y	Y
21	K	13.0	M	26-09-2007	1.0	U	56	SDNS	1	N	Y	0.85	4	Y	Y	Y	Y
22	BS	10.0	M	26-07-2001	0.8	U	76	SDNS	1	N	N	1.4	1	N	N	N	N
23	K	5.3	M	24-10-2013	5.2	U	438	SRNS	2	N	N		0	N	N	N	N
24	W	6.0	M	24-08-2013	6.0	R	450	SRNS	2	N	N		0	N	N	N	N
25	RP	3.8	M	11-01-2018	3.8	U	470	SRNS	2	N	N		4	Y	N	N	N
26	MS	7.0	M	19-08-2013	6.0	R	516	SRNS	2	Y	N		3	N	N	N	N
27	PK	10.0	M	10-06-2000	0.9	U	96	SRNS	2	N	N		4	Y	N	Y	Y

Sr. No.	Name	Age (YEARS)	Cyclosporin (Y/N)	Status Of Patient At Start Of Tacrolimus CR/PR/NR	Steroid Toxicty	Cataract	Cushingoid	Short Stature	Hypertension	Overweight	Obesity	Behavior	Renal Biopsy Findings (Year)	Tacrolimus Administration & Parameters Detail	Age At Start Of Tacrolimus	Duration Of NS (Months) (Age of onset of NS MINUS Age of start of Tacrolimus)	Age (Yrs.)	Weight (KG)	Weight z score
1	SN	4.0	N	CR	Y	N	N	Y	Y	N	Y	Y	N	22-04-2015	4.1	2	4.2	17.7	0.5
2	AS	7.0	N	CR	Y	N	N	Y	Y	Y	N	N	N	14-09-2016	7.0	22	7.0	20.0	-1.1
3	AS	8.0	N	CR	Y	N	Y	N	Y	N	N	N	N	24-12-2021	8.4	30	8.5	25.5	-0.4
4	GS	4.0	N	CR	Y	N	Y	N	Y	N	Y	N	N	08-10-2021	4.6	7	4.7	28.0	2.9
5	E	5.0	N	CR	Y	N	N	N	Y	N	Y	N	N	03-01-2022	6.0	32	6.0	25.0	1.2
6	ES	5.0	N	CR	Y	N	N	Y	Y	N	Y	N	N	23-08-2021	5.0	30	5.0	17.6	-0.4
7	GK	3.0	N	CR	Y	N	N	N	Y	N	N	N	N	16-04-2021	2.0	8	2.0	12.3	-0.3
8	DJ	12.8	N	CR	Y	N	Y	N	N	Y	N	N	N	24-07-2021	12.6	44	12.8	60.0	1.3
9	R	1.6	N	CR	Y	N	N	N	N	N	Y	N	N	27-07-2020	2.1	7	2.1	13.0	0.1
10	KP	6.5	N	CR	N	N	N	N	N	N	N	N	N	18-09-2020	5.4	12	5.5	15.5	-1.7
11	OS	11.0	N	CR	N	N	N	N	N	N	N	N	FSGS	16-12-2019	12.0	12	11.0	26.9	-1.8
12	H	4.0	N	CR	Y	N	Y	Y	N	N	N	N	N	30-10-2017	4.8	16	4.8	13.8	-2.0
13	GK	7.0	N	CR	N	N	N	N	N	N	N	N	N	24-11-2017	8.5	8	8.5	18.7	-2.6
14	M	2.0	N	CR	N	N	N	N	N	N	N	N	N	30-11-2016	2.0	6	2.0	12.0	-0.6
15	H	9.0	Y	CR	N	N	N	N	N	N	N	N	MCNS	29-05-2019	8.5	66	8.5	29.7	0.5
16	G	5.0	N	CR	Y	N	Y	N	N	N	Y	N	N	10-02-2016	5.6	20	5.7	24.0	1.2
17	S	9.4	N	CR	Y	N	N	Y	N	N	N	N	N	25-10-2021	9.4	102	9.4	27.8	-0.4
18	S	5.5	N	CR	Y	N	N	N	Y	N	N	N	N	14-10-2015	5.5	42	5.5	18.7	-0.4
19	JS	17.0	Y	CR	Y	N	Y	N	N	N	Y	N	MCNS	23-12-2013	8.0	4	8.0	38.6	2.0
20	IS	13.0	N	CR	N	N	N	N	N	N	N	N	MCNS	22-10-2014	7.0	74	7.0	24.1	0.2
21	K	13.0	N	CR	N	N	N	N	N	N	N	N	MCNS	11-10-2014	7.0	73	7.0	22.0	-0.4
22	BS	10.0	N	CR	Y	N	Y	N	N	N	N	N	MCNS	13-08-2010	10.0	1	10.0	25.4	-1.5
23	K	5.3	N	NR	Y	N	N	Y	Y	N	N	N	N	08-02-2019	5.3	2	5.3	16.6	-1.1
24	W	6.0	N	NR	Y	N	N	N	Y	N	Y	N	N	15-04-2019	6.0	1	6.0	20.0	-0.4
25	RP	3.8	Y	NR	Y	N	N	Y	Y	N	N	N	N	15-11-2021	4.9	43	4.9	14.8	-1.7
26	MS	7.0	N	NR	N	N	N	N	N	N	N	N	N	29-06-2020	6.8	10	6.8	19.5	-1.1
27	PK	10.0	N	PR	Y	N	N	N	Y	N	Y	N	MCNS	28-10-2015	15.0	168	15.0	44.0	-1.5

Sr. No.	Name	Age (YEARS)	Height (CM)	Height z score	BMI	BMI z score	Sr Creatinine	Dose Given (STARTING DOSE) (Mg/Kg)	Associated Medications	ENVAS	Side effects of Tacrolimus: (Tick/Yes/No)	Hypertension	Hyperkalemia	Seizure	Increase Blood Sugar	Increase OT/ PT	Diarrhea	UTI	Reversible Nephropathy
1	SN	4.0	95	-2.0	19.6	2.6	N	0.05	LABETALOL ENVAS AMLONG	Y		N	N	N	N	N	N	N	N
2	AS	7.0	107	-2.8	17.5	1.1	N	0.15	ENVAS	Y		N	N	N	N	N	N	N	N
3	AS	8.0	129	-0.3	15.3	15.3	N	0.12	ENVAS	Y		N	N	N	N	N	N	N	N
4	GS	4.0	105	-0.4	25.3	4.0	N	0.05	ENVAS	Y		N	N	N	N	N	N	N	N
5	E	5.0	111	-0.9	20.3	2.2	N	0.08	ENVAS	Y		N	N	N	N	N	N	N	N
6	ES	5.0	93	-3.4	20.3	2.6	N	0.10	ENVAS	Y		N	N	N	N	N	N	N	N
7	GK	3.0	82	-1.4	18.3	1.1	N	0.08	ENVAS	Y		N	N	N	N	N	N	N	N
8	DJ	12.8	153	-0.4	25.6	1.6	N	0.08	-	N		N	N	N	N	N	N	N	N
9	R	1.6	80	-2.2	20.3	2.2	N	0.08	-	N		N	N	N	N	N	N	N	N
10	KP	6.5	105	-1.3	14.1	-1.0	N	0.10	ENVAS	Y		Y	N	N	N	N	N	N	N
11	OS	11.0	136	-1.1	14.5	1.7	N	0.06	ENVAS	Y		N	N	N	N	N	N	N	N
12	H	4.0	93	-3.0	16	0.6	N	0.10	ENVAS	Y		N	N	N	N	N	N	N	N
13	GK	7.0	112	-3.3	14.9	14.9	N	0.10	ENVAS SPIRONOLACTONE	Y		Y	N	N	N	N	N	N	N
14	M	2.0	80	-2.0	18.7	1.4	N	0.04	-	N		N	N	N	N	N	N	N	N
15	H	9.0	128	-0.5	18.1	1.0	N	0.10	ENVAS	Y		N	N	N	N	N	N	N	N
16	G	5.0	109	-0.7	20.2	2.1	N	0.04	ENVAS	Y		N	N	N	N	N	N	N	N
17	S	9.4	127	-1.4	17.2	0.4	N	0.10	ENVAS	Y		Y	N	N	N	N	Y	N	N
18	S	5.5	107	-1.1	16.3	0.7	N	0.05	ENVAS	Y		N	N	N	N	N	N	N	N
19	JS	17.0	133	0.8	21.8	2.0	N	0.15	ENVAS	Y		Y	N	N	N	N	N	Y	N
20	IS	13.0	121	-0.2	16.5	0.6	N	0.30	ENVAS	Y		N	N	N	N	N	N	N	Y
21	K	13.0	124	0.4	14.3	-1.0	N	0.30	ENVAS	Y		N	N	N	N	N	N	N	N
22	BS	10.0	141	0.3	12.8	-3.2	N	0.08	ENVAS	Y		Y	N	N	N	N	N	N	N
23	K	5.3	97	-2.9	17.6	1.4	N	0.12	WYSOLONE,ENVAS	Y		Y	N	N	N	N	N	N	N
24	W	6.0	98	-3.6	20.8	2.3	N	0.10	AMLONG, ENVAS, ELTROXIN	Y		Y	N	N	N	N	N	Y	N
25	RP	3.8	100	-1.7	14.8	-0.6	N	0.13	ENVAS	Y		N	N	N	N	N	N	N	N
26	MS	7.0	118	-0.6	14	-1.3	N	0.10	PREDNISOLONE,ENVAS	Y		N	N	N	N	N	N	N	N
27	PK	10.0	145	-3.4	22.1	0.7	N	0.13	WYSOLONE ENVAS	Y		N	N	N	N	N	Y	N	N

Sr. No.	Name	Age (YEARS)	Hypertrichosis	Gingival Hyperplasia	Acne	Skin infections	Major infection (Requiring hospitalization) Diagnosis	Others	Urine albumin 1M	Urine albumin 3M	Urine albumin 6M	Urine albumin 9M	Urine albumin 12M	TACROLIMUS LEVELS 1M	TACROLIMUS LEVELS 3M	TACROLIMUS LEVELS 6M	TACROLIMUS LEVELS 9M
1	SN	4.0	N	N	N	N	N	N	1	0	0	0	0		4.8		2.56
2	AS	7.0	N	N	N	N	N	N	0	0	0	0	0	1.24	3.65	3.43	5.16
3	AS	8.0	N	N	N	N	N	N	0	0	0	0	0	6.68	12.1	5.62	2.48
4	GS	4.0	N	N	N	N	N	N	0	0	0	0	0	9.96	5.1	5.06	
5	E	5.0	N	N	N	N	N	N	0	0	0	0	0	3.3	3.94	4.35	3.76
6	ES	5.0	N	N	N	N	N	N	0	0	0	0	0	3.82	2.9	2.75	3.05
7	GK	3.0	N	N	N	N	N	N	0	0	0	0	0	2.2	2.21	5.3	5.13
8	DJ	12.8	N	N	N	Y	N	N	0	0	0	0	0	7.79	7.3	4.81	2.56
9	R	1.6	N	N	N	N	N	N	0	0	0	0	0	1.78	2.42	6.06	0
10	KP	6.5	N	N	N	N	N	N	1	0	0	0	0	5.32	3.5	2.02	3.93
11	OS	11.0	N	N	N	N	N	N	TRACE	TRACE	0	0	0				2.32
12	H	4.0	N	N	N	N	N	N	2	1	0	0	0				6.72
13	GK	7.0	N	N	N	Y	PNEUMONIA, PNEUMONIA BRONCHIOLITIS	N	2	2	2	2	2			3.2	
14	M	2.0	N	N	N	N	N	N	TRACE	0	0	0	0		8.3	4.2	4.51
15	H	9.0	N	N	N	N	N	N	0	0	0	0	0			4.7	2
16	G	5.0	N	N	N	N	N	N	TRACE	TRACE	0	0	0			5.2	
17	S	9.4	N	N	N	N	N	N	0	0	2	TRACE	0		4.31	1.5	4.16
18	S	5.5	N	N	N	N	N	N	0	0	0	0	0		7.28		
19	JS	17.0	N	N	N	N	N	N	2	2	2	2	2			12	
20	IS	13.0	N	N	N	N	N	N	1	0	0	0	0		3.27		
21	K	13.0	N	N	N	N	N	N	1	0	0	0	0		3.2		
22	BS	10.0	N	N	N	N	N	N	1	0	3	3	3			4.8	
23	K	5.3	N	N	N	N	N	N	TRACE	0	0	1	2			4.42	
24	W	6.0	N	N	N	N	PNEUMONIA BRONCHIOLITIS	Y	3	3	3	3	3				3.9
25	RP	3.8	N	N	N	N	N	N	0	0	0	0	0	1.45	2.51	1	5.52
26	MS	7.0	N	N	N	N	N	N	3	2	0	0	0			2.19	3.58
27	PK	10.0	N	N	N	N	PNEUMONIA	N	2	0	TRACE	0	0		6.13		

Sr. No.	Name	Age (YEARS)	TACROLIMUS LEVELS 12M	TACROLIMUS LEVELS	No. of times TAC levels done	Edema	EDEMA 3M	EDEMA 6M	EDEMA 9M	EDEMA 12M	At 6 Months CR/PR/NR	At 12 Months (CR/PR/NR)	Tacrolimus Given For Duration (Months)	Off Steroids (Y/N) In SDNS/FRNS)	DURATION TAKEN TO GET OFF STEROID POST TAC	If Yes, Duration Off Steroids
1	SN	4.0		3.7	2.0	0	0	0	0	0	CR	CR	14	Y	6	6
2	AS	7.0	7.1	4.1	5.0	0	0	0	0	0	CR	CR	18	Y	9	3
3	AS	8.0	6.25	6.6	5.0	0	0	0	0	0	CR	CR	12	Y	7	5
4	GS	4.0	4.02	6.0	4.0	0	0	0	0	0	CR	CR	13	Y	5	7
5	E	5.0	2.86	3.6	5.0	0	0	0	0	0	CR	CR	12	Y	4	8
6	ES	5.0	3.81	3.3	5.0	0	0	0	0	0	CR	CR	15	Y	4	8
7	GK	3.0	4.9	3.9	5.0	0	1	0	0	0	CR	CR	14	Y	7	5
8	DJ	12.8	2.33	5.0	5.0	0	0	0	0	0	CR	CR	16	Y	5	7
9	R	1.6	4.51	3.0	4.0	0	0	0	0	0	CR	CR	28	Y	5	7
10	KP	6.5	5.81	4.1	5.0	0	0	0	0	0	CR	CR	14	Y	6	6
11	OS	11.0		2.3	1.0	1	0	0	0	0	CR	CR	48	Y	4	8
12	H	4.0		6.7	1.0	2	2	2	0	0	PR	CR	36	N		
13	GK	7.0		3.2	1.0	2	2	2	2	2	PR	CR	15	N		
14	M	2.0		5.7	3.0	1	0	0	0	0	CR	CR	18	N		
15	H	9.0	2.94	3.2	3.0	0	0	0	0	0	CR	CR	23	Y	10	2
16	G	5.0		5.2	1.0	0	0	0	0	0	CR	CR	60	Y	11	1
17	S	9.4	6.16	4.0	4.0	0	0	0	0	0	CR	CR	14	N		
18	S	5.5	6.36	6.8	2.0	0	0	0	0	0	CR	CR	12	Y	10	2
19	JS	17.0		12.0	1.0	0	0	0	0	0	NR	NR	12	N		
20	IS	13.0		3.3	1.0	1	0	0	0	0	CR	CR	51	Y	8	4
21	K	13.0		3.2	1.0	1	0	0	0	0	CR	CR	50	Y	8	4
22	BS	10.0		4.8	1.0	1	0	2	2	2	CR	PR	36	N		
23	K	5.3		4.4	1.0	0	0	0	1	1	CR	CR	24	N		
24	W	6.0		3.9	1.0	2	5	3	3	3	NR	NR	12	N		
25	RP	3.8	6.72	3.4	5.0	0	0	0	0	0	CR	CR	14	Y	4	8
26	MS	7.0	4.46	3.4	3.0	1	1	1	0	0	CR	CR	30	Y	12	0
27	PK	10.0		6.1	1.0	1	0	0	0	0	CR	CR	14	N		

Sr. No.	Name	Age (YEARS)	If No, Steroid Dependent Dose	First Relapse (Months after starting Tacrolimus)		No. Of Relapses After Starting Tacrolimus (In 12 Months Peroid)	Sr Creatinine at stopping Tacrolimus	Age (Yrs) after 1yr	Weight (KG) after 1yr	Weight z score after 1yr	Diff Weight Z	Height (CM) after 1yr	HEIGHT z score after 1yr	Diff HEIGHT Z	BMI after 1yr	BMI z score after 1yr	Diff BMI Z
1	SN	4.0			1		NOT STOPPED	5.0	16	-1.4	-1.8	102	-1.7	0.3	15.4	0.0	-2.6
2	AS	7.0			1		NOT STOPPED	8.0	19	-2.4	-1.3	114	-2.5	0.3	13.7	-1.8	-2.9
3	AS	8.0			1		NOT STOPPED	9.5	30	-0.1	0.4	140	0.6	0.9	15.3	-0.7	-16.0
4	GS	4.0			1		NOT STOPPED	5.7	26	1.7	-1.2	112	-0.3	0.1	20.7	2.4	-1.6
5	E	5.0			1		NOT STOPPED	7.0	24	0.2	-1.0	120	-0.4	0.5	16.7	0.7	-1.5
6	ES	5.0			1		NOT STOPPED	6.0	18	-1.1	-0.7	106	-1.9	1.5	16	0.5	-2.1
7	GK	3.0			1		NOT STOPPED	3.0	13.5	-0.6	-0.3	94	-0.3	1.1	15.3	-0.7	-1.8
8	DJ	12.8			1		NOT STOPPED	14.0	53	0.4	-0.9	157	-0.4	0.0	21.5	0.7	-0.9
9	R	1.6			1		NOT STOPPED	3.1	11.5	-2.3	-2.3	91	-1.3	0.9	13.9	-2.1	-4.3
10	KP	6.5		9	3	2	NORMAL	6.5	17.9	-1.4	0.3	113	-1.0	0.3	14	-1.0	0.0
11	OS	11.0		6	2	2	NOT STOPPED	12.0	40	-0.9	0.9	156	0.9	2.0	16.4	-0.7	-2.4
12	H	4.0	0.9	2	2	4	NOT STOPPED	5.8	14	-3.0	-1.0	100	-2.8	0.2	14	-1.0	-1.6
13	GK	7.0	0.5	3	2	4	NOT STOPPED	9.5	21	-2.5	0.2	114	-3.6	-0.3	16.2	-0.2	-15.1
14	M	2.0	0.3	2	2	2	NOT STOPPED	3.0	13.1	-0.9	-0.3	88.5	-1.8	0.2	16.7	0.6	-0.8
15	H	9.0		1	2	1	NOT STOPPED	9.5	33	0.5	-0.1	137	0.1	0.6	17.6	0.5	-0.5
16	G	5.0			1		NOT STOPPED	6.7	23.8	0.5	-0.7	123	0.6	1.3	15.7	0.2	-1.9
17	S	9.4	0.6		1		NOT STOPPED	10.5	27	-1.4	-1.0	130	-1.7	-0.3	16	-0.5	-0.9
18	S	5.5			1		NORMAL	6.5	24.6	0.7	1.1	121	0.4	1.5	16.8	0.8	0.1
19	JS	17.0	0.5	3	2	3	NORMAL	9.0	40.8	1.7	-0.3	135	0.2	-0.6	22.4	1.9	-0.1
20	IS	13.0			1		NOT STOPPED	8.0	26.2	0.1	-0.1	125	-0.5	-0.3	16.8	0.5	-0.1
21	K	13.0			1		NOT STOPPED	8.0	27	0.3	0.7	127	-0.2	-0.6	16.1	0.5	1.5
22	BS	10.0	1	11	3	4	NOT STOPPED	11.0	29.1	-1.3	0.3	150	0.9	0.6	12.9	-3.3	-0.1
23	K	5.3	0.3	10	3	1	NOT STOPPED	6.4	17.5	-1.5	-0.4	109	-1.7	1.2	14.7	-0.6	-2.0
24	W	6.0	1.7	1	2	5	NOT STOPPED	7.0	17.8	-2.0	-1.7	102	-3.8	-0.3	17.4	1.0	-1.3
25	RP	3.8			1		NOT STOPPED	5.9	16.4	-1.8	-0.1	106	-1.6	0.1	14.6	-0.7	-0.1
26	MS	7.0		2	2	2	NOT STOPPED	8.0	19	-2.1	-1.0	124	-0.4	0.2	12.4	-3.6	-2.3
27	PK	10.0	0.47	10	3	1	NOT STOPPED	16.0	37.6	-3.3	-1.8	145	-3.5	-0.2	17.9	-1.2	-1.9

Sr. No.	Name	Age (YEARS)	OBESITY at 1yr	Short stature at 1yr	Sr Creatinine after 1yr	Sr Albumin after 1yr	RESPONDER/ NON RESPONDER (R / NR)	Treatment Failure (Y/N)	CAUSE OF TREATMENT FAILURE. >/=3 RELAPSES	Recurrence of SR (no response after relapse, after 4 weeks full dose steroids) (Y/N)	Irreversible increase in Sr Creatinine (< 50 ml/min/ 1.73m2) (Y/N)	Tacrolimus Stopped (Y/N)	Reason Of Stopping	Drug Started (Rituximab) (Y/N)	Date Started
1	SN	4.0	N	N	N	N	R	N	NA	N	N	N	-	N	-
2	AS	7.0	N	Y	N	N	R	N	NA	N	N	N	-	N	-
3	AS	8.0	N	N	N	N	R	N	NA	N	N	N	-	N	-
4	GS	4.0	N	N	N	N	R	N	NA	N	N	N	-	N	-
5	E	5.0	N	N	N	N	R	N	NA	N	N	N	-	N	-
6	ES	5.0	N	N	N	N	R	N	N	N	N	N	-	N	-
7	GK	3.0	N	N	N	N	R	N	N	N	N	N	-	N	-
8	DJ	12.8	N	N	N	N	R	N	N	N	N	N	-	N	-
9	R	1.6	Y	N	N	N	R	N	N	N	N	N	-	N	-
10	KP	6.5	N	N	N	N	R	N	N	N	N	Y	FREQUENT RELAPSER	N	-
11	OS	11.0	N	N	N	N	R	N	N	N	N	N	-	N	-
12	H	4.0	N	Y	N	N	NR	Y	Y	N	N	N	-	Y	11TH MONTH
13	GK	7.0	N	Y	N	LOW	NR	Y	Y	N	N	N	-	N	-
14	M	2.0	N	N	N		R	N	N	N	N	N	-	N	-
15	H	9.0	N	N	N		R	N	N	N	N	N	-	N	-
16	G	5.0	N	N	N		R	N	N	N	N	N	-	N	-
17	S	9.4	N	N	N	N	R	N	N	N	N	N	-	N	-
18	S	5.5	N	N	N	N	R	N	N	N	N	Y	OFF TREATMENT	N	-
19	JS	17.0	N	N	N		NR	Y	Y	Y	N	Y	POOR RESPONSE	Y	14-07-2014
20	IS	13.0	N	N	N	N	R	N	N	N	N	N	-	N	-
21	K	13.0	N	N	N	N	R	N	N	N	N	N	-	N	-
22	BS	10.0	Y	N	N	N	NR	Y	Y	Y	N	N	-	N	-
23	K	5.3	N	N	N	N	R	N	N	N	N	N	-	N	-
24	W	6.0	N	Y	N	LOW	NR	Y	Y	Y	N	N	-	N	-
25	RP	3.8	N	N	N	N	R	N	N	N	N	N	-	N	-
26	MS	7.0	Y	N	N		R	N	N	N	N	N	-	N	-
27	PK	10.0	N	Y	N		R	N	N	N	N	N	-	N	-

Sr. No.	Name	Age (YEARS)	Response At 6 Months Post Rituximab (CR/PR/NR	serum albumin 0	S Albumin 1	S Albumin 6	S Albumin 12	Diff S Albumin 1	Diff S Albumin 6	Diff S Albumin 12	s.creat 0 M	s.creat 1 M	S CREAT 6 M	S CREAT 12M	Diff s.creat 1 M	Diff S CREAT 6 M	Diff S CREAT 12M
1	SN	4.0	-	2.6	2.64	3	3.34	0.04	0.4	0.74	0.38	0.4	0.38	0.44	0.02	0	0.06
2	AS	7.0	-	2.74	2.8	2.9	3.2	0.06	0.16	0.46	0.36	0.38	0.34	0.36	0.02	-0.02	0
3	AS	8.0	-	2.6	3	3.2	3.86	0.4	0.6	1.26	0.32	0.32	0.34	0.36	0	0.02	0.04
4	GS	4.0	-	3.1	3.2	3.8	4.02	0.1	0.7	0.92	0.34	0.3	0.3	0.34	-0.04	-0.04	0
5	E	5.0	-	2.74	3	3.1	3.22	0.26	0.36	0.48	0.31	0.36	0.34	0.38	0.05	0.03	0.07
6	ES	5.0	-	3.32	3.2	3.3	3.5	-0.12	-0.02	0.18	0.38	0.4	0.38	0.42	0.02	0	0.04
7	GK	3.0	-	2.7	2.76	2.9	3	0.06	0.2	0.3	0.4	0.38	0.42	0.4	-0.02	0.02	0
8	DJ	12.8	-	2.65	2.9	3.1	3.2	0.25	0.45	0.55	0.4	0.42	0.39	0.38	0.02	-0.01	-0.02
9	R	1.6	-	2.54	2.66	3.2	4	0.12	0.66	1.46	0.36	0.38	0.33	0.44	0.02	-0.03	0.08
10	KP	6.5	-	2.88	3.2	3.4	3.6	0.32	0.52	0.72	0.42	0.41	0.39	0.36	-0.01	-0.03	-0.06
11	OS	11.0	-	2.9	3.3	3.2	3.38	0.4	0.3	0.48	0.38	0.42	0.4	0.38	0.04	0.02	0
12	H	4.0	NR	2.26	2.9	3.6	4.2	0.64	1.34	1.94	0.36	0.38	0.42	0.4	0.02	0.06	0.04
13	GK	7.0	-	2.9	3.1	3.4	4.2	0.2	0.5	1.3	0.42	0.44	0.4	0.38	0.02	-0.02	-0.04
14	M	2.0	-	3.3	3.1	3.8	4.4	-0.2	0.5	1.1	0.2	0.2	0.28	0.3	0	0.08	0.1
15	H	9.0	-	3.8	3.4	4	4.2	-0.4	0.2	0.4	0.36	0.4	0.38	0.38	0.04	0.02	0.02
16	G	5.0	-	2.6	2.9	3.2	3.8	0.3	0.6	1.2	0.33	0.34	0.4	0.42	0.01	0.07	0.09
17	S	9.4	-	3.9	3.8	4	4.2	-0.1	0.1	0.3	0.4	0.42	0.44	0.36	0.02	0.04	-0.04
18	S	5.5	-	3.1	3.3	3	3.1	0.2	-0.1	0	0.34	0.36	0.29	0.33	0.02	-0.05	-0.01
19	JS	17.0	NR	2.8	2.5	3	1.8	-0.3	0.2	-1	0.42	0.44	0.36	0.4	0.02	-0.06	-0.02
20	IS	13.0	-	2.6	2.6	2.8	2.9	0	0.2	0.3	0.26	0.28	0.3	0.32	0.02	0.04	0.06
21	K	13.0	-	2.76	2.84	3	3.1	0.08	0.24	0.34	0.38	0.38	0.36	0.38	0	-0.02	0
22	BS	10.0	-	2.8	2.76	3	2.4	-0.04	0.2	-0.4	0.4	0.42	0.4	0.4	0.02	0	0
23	K	5.3	-	1.49	3.55	3.99	3.1	2.06	2.5	1.61	0.43	0.45	0.38	0.33	0.02	-0.05	-0.1
24	W	6.0	-	1.24	2.2	2.9	2.2	0.96	1.66	0.96	0.18	0.18	0.29	0.43	0	0.11	0.25
25	RP	3.8	-	1.64	3.4	3.6	2.9	1.76	1.96	1.26	0.3	0.32	0.23	0.37	0.02	-0.07	0.07
26	MS	7.0	-	1.4	2.8	3.16	3	1.4	1.76	1.6	0.32	0.34	0.3	0.28	0.02	-0.02	-0.04
27	PK	10.0	-	1.88	2.54	3.1	3.4	0.66	1.22	1.52	0.6	0.6	0.42	0.39	0	-0.18	-0.21

Sr. No.	Name	Age (YEARS)	Sex	Date of birth	Age Of Onset (Year / Month)	Urban/ Rural	File No. (Ped. Nephro)	Diagnosis (FRNS/SDNS/ SRNS)	Group	Hypertension at onset (Y/N)	Microscopic Haematuria at onset (Y/N)	Dependent Dose (Mg/Kg/Day) (If SDNS)	No Of Relapse Last One Year (Before Tacrolimus)	Prior Immunosuppressives	Levamisole (Y/N)	Cyclophosphamide (Y/N)	Mycophenolate (Y/N)
28	AS	2.0	M	28-09-2014	1.5	U	345	SRNS	2	Y	N		0	Y	N	N	N
29	SS	3.0	M	21-01-2018	2.6	R	531	SRNS	2	Y	N		0	N	N	N	N
30	S	10.0	F	07-11-2022	10.0	U	602	SRNS	2	N	N		0	N	N	N	N
31	BT	5.3	M	15-06-2015	4.5	U	523	SRNS	2	N	N		0	N	N	N	N
32	K	4.4	M	10-02-2016	4.5	U	522	SRNS	2	N	N		0	N	N	N	N
33	DJ	5.5	F	22-01-2016	4.0	U	440	SRNS	2	Y	N		3	Y	N	N	N
34	JS	4.0	M	30-06-2014	4.0	R	411	SRNS	2	Y	Y		0	N	N	N	N
35	G	5.0	M	21-01-1900	4.0	U	21	SRNS	2	N	N		0	N	N	N	N
36	B	6.0	M	21-11-2014	2.0	U	563	SRNS	2	N	N		0	N	N	N	N
37	GK	9.0	F	22-04-2010	5.0	U	508	SRNS	2	N	N		2	N	N	N	N
38	P	3.6	M	05-02-2014	3.0	U	357	SRNS	2	N	N		3	Y	N	N	N
39	R	3.0	F	15-12-2014	2.9	U	392	SRNS	2	N	N		1	N	N	N	N
40	R	2.0	M	09-09-2016	2.0	U	416	SRNS	2	N	N		0	N	N	N	N
41	R	3.0	M	07-10-2015	3.0	U	600	SRNS	2	N	N		0	N	N	N	N
42	M	5.5	F	30-12-2015	4.0	U	336	SRNS	2	Y	N		3	N	N	N	N
43	PM	4.1	M	01-03-2018	2.8	U	600	SRNS	2	Y	N		0	N	N	N	N

Sr. No.	Name	Age (YEARS)	Cyclosporin (Y/N)	Status Of Patient At Start Of Tacrolimus CR/PR/NR	Steroid Toxicty	Cataract	Cushingoid	Short Stature	Hypertension	Overweight	Obesity	Behavior	Renal Biopsy Findings (Year)	Tacrolimus Administration & Parameters Detail	Age At Start Of Tacrolimus	Duration Of NS (Months) (Age of onset of NS MINUS Age of start of Tacrolimus)	Age (Yrs.)	Weight (KG)	Weight z score
28	AS	2.0	Y	NR	Y	N	Y	Y	N	N	Y	N	FSGS	28-08-2017	2.9	11	2.9	13.7	-0.4
29	SS	3.0	N	NR	Y	N	N	N	Y	N	Y	N	N	10-11-2020	3.0	2	3.0	16.8	1.3
30	S	10.0	N	NR	Y	N	N	Y	Y	N	N	N	MCNS	28-05-2022	10.0	4	10.0	23.0	-2.3
31	BT	5.3	N	NR	Y	N	Y	N	N	N	N	N	N	26-06-2020	5.0	4	5.2	16.0	-1.4
32	K	4.4	N	NR	Y	N	N	N	Y	N	Y	N	N	04-05-2020	4.5	6	4.5	20.0	1.1
33	DJ	5.5	Y	NR	Y	N	Y	N	N	N	N	N	N	24-07-2020	5.5	18	5.5	17.3	-0.8
34	JS	4.0	N	NR	Y	N	Y	N	Y	N	N	N	N	27-07-2018	4.0	2	4.0	16.4	0.0
35	G	5.0	N	NR	Y	N	N	N	Y	N	N	N	MCNS	24-03-2009	4.0	12	4.0	18.5	1.0
36	B	6.0	N	NR	Y	N	N	N	Y	N	N	N	FSGS	27-08-2021	6.5	48	6.5	22.5	0.2
37	GK	9.0	N	NR	N	N	N	N	N	N	N	N	FSGS	18-08-2020	9.0	48	9.0	23.0	-1.4
38	P	3.6	Y	NR	Y	N	Y	N	N	N	N	N	MCNS	13-09-2017	3.5	7	3.6	15.4	0.6
39	R	3.0	N	NR	Y	N	Y	N	N	N	N	N	N	26-02-2018	3.1	2	3.1	12.7	-1.6
40	R	2.0	N	NR	N	N	N	N	N	N	N	N	N	17-10-2018	2.0	1	2.0	10.8	-1.7
41	R	3.0	N	NR	N	N	N	N	N	N	N	N	N	07-11-2019	3.0	1	3.0	12.0	-1.7
42	M	5.5	Y	NR	Y	N	Y	N	N	N	N	N	N	20-06-2020	5.7	20	5.7	19.4	-0.1
43	PM	4.1	N	NR	Y	N	N	N	Y	N	N	N	N	02-02-2022	3.9	9	3.9	12	-2.75

Sr. No.	Name	Age (YEARS)	Height (CM)	Height z score	BMI	BMI z score	Sr Creatinine	Dose Given (STARTING DOSE) (Mg/Kg)	Associated Medications	ENVAS	Side effects of Tacrolimus: (Tick/Yes/No)	Hypertension	Hyperkalemia	Seizure	Increase Blood Sugar	Increase OT/ PT	Diarrhea	UTI	Reversible Nephropathy
28	AS	2.0	81	-3.9	20.9	3.0	N	0.14	ENVAS	Y		N	N	N	N	N	Y	N	N
29	SS	3.0	93	-0.6	19.3	2.3	N	0.10	ENVAS	Y		N	N	N	N	N	Y	N	N
30	S	10.0	126	-2.0	15.6	-1.3	N	0.30	ENVAS	Y		N	N	N	N	N	N	N	N
31	BT	5.3	101	-2.0	15.6	0.2	N	0.06	ENVAS	Y		Y	N	N	N	N	Y	N	N
32	K	4.4	100	-1.3	20	2.7	N	0.06	ENVAS	Y		Y	N	N	N	N	N	Y	N
33	DJ	5.5	104	-1.6	16	0.6	N	0.05	-	N		Y	N	N	N	N	N	N	N
34	JS	4.0	96	-1.6	17.8	1.6	N	0.05	ENVAS	Y		Y	N	N	N	N	N	Y	N
35	G	5.0	112	2.2	14.7	-0.8	N	0.10	ENVAS	Y		N	N	N	N	N	N	N	N
36	B	6.0	111	-1.3	1.5	1.5	N	0.10	ENVAS	Y		Y	N	N	N	N	N	N	N
37	GK	9.0	125	-1.3	14.7	-0.9	N	0.10	ENVAS	y		Y	N	N	N	N	N	N	N
38	P	3.6	96	0.2	16.7	0.6	N	0.10	ENVAS	Y		Y	N	N	N	N	N	N	N
39	R	3.0	96	-0.6	13.9	-1.8	N	0.07	ENVAS	Y		Y	N	N	N	N	N	N	N
40	R	2.0	84	-1.0	15.3	-1.0	N	0.08	ENVAS	Y		Y	N	N	N	N	N	N	N
41	R	3.0	92	-0.9	14.2	-1.8	N	0.10	ENVAS	Y		Y	N	N	N	N	N	N	N
42	M	5.5	107	-1.2	16.9	1.0	N	0.10	ENVAS	Y		Y	N	N	N	N	N	N	N
43	PM	4.1	98	-2.8	12.5	-3.8	N	0.1	ENVAS	Y		N	N	N	N	N	N	N	N

Sr. No.	Name	Age (YEARS)	Hypertrichosis	Gingival Hyperplasia	Acne	Skin infections	Major infection (Requiring hospitalization) Diagnosis	Others	Urine albumin 1M	Urine albumin 3M	Urine albumin 6M	Urine albumin 9M	Urine albumin 12M	TACROLIMUS LEVELS 1M	TACROLIMUS LEVELS 3M	TACROLIMUS LEVELS 6M	TACROLIMUS LEVELS 9M
28	AS	2.0	N	N	N	N	PNEUMONIA	URI	3	2	2	2	2			4.7	7.82
29	SS	3.0	N	N	N	N	N	N	3	3	2	1	2	1.25	4.47	3.88	4.31
30	S	10.0	N	N	N	N	N	N	1	1	4	3	2	1.76	3.56	3.67	
31	BT	5.3	N	N	N	N	N	N	TRACE	TRACE	TRACE	0	0		1.8	2.44	1.85
32	K	4.4	N	N	N	N	N	N	2	1	2	3	1	2.10		5.08	1.75
33	DJ	5.5	N	N	N	N	N	N	2	TRACE	TRACE	TRACE	0			1.47	2.18
34	JS	4.0	N	N	N	N	N	N	2	2	2	2	2				2.9
35	G	5.0	N	N	N	N	N	N	2	1	0	1	0	1		1.8	
36	B	6.0	N	N	N	N	N	N	2	1	TRACE	0	0	1.59	3.58	2.38	3.89
37	GK	9.0	N	N	N	N	N	N	4	3	2	2	1	3.52		4.42	
38	P	3.6	N	N	N	N	N	N	0	0	0	0	0		3.65	5.36	4.97
39	R	3.0	N	N	N	N	N	N	0	0	0	0	0		2.09		
40	R	2.0	N	N	N	N	N	N	0	0	0	0	0	1.8	1.67	3.17	2.82
41	R	3.0	N	N	N	N	N	N	2	3	2	2	1	1.7	1.8	3.2	2.86
42	M	5.5	N	N	N	N	N	N	2	TRACE	TRACE	TRACE	NIL			1.52	2.2
43	PM	4.1	N	N	N	N	N	N	3	0	0	0	0	4.9		4.89	13

Sr. No.	Name	Age (YEARS)	TACROLIMUS LEVELS 12M	TACROLIMUS LEVELS	No. of times TAC levels done	Edema	EDEMA 3M	EDEMA 6M	EDEMA 9M	EDEMA 12M	At 6 Months CR/PR/NR	At 12 Months (CR/PR/NR)	Tacrolimus Given For Duration (Months)	Off Steroids (Y/N) In SDNS/FRNS)	DURATION TAKEN TO GET OFF STEROID POST TAC	If Yes, Duration Off Steroids
28	AS	2.0	3.3	5.3	3.0	1	2	1	1	1	NR	NR	39	N		
29	SS	3.0	3	3.4	5.0	3	2	2	3	2	NR	NR	24	N		
30	S	10.0		3.0	3.0	1	0	2	2	1	NR	NR	13	N		
31	BT	5.3	5.05	2.8	4.0	0	0	0	0	0	CR	CR	30	Y	10	2
32	K	4.4	5.00	3.5	4.0	1	0	2	3	1	NR	PR	30	N		
33	DJ	5.5	3.85	2.5	3.0	1	1	1	0	0	PR	CR	27	N		
34	JS	4.0		2.9	1.0	2	1	1	1	1	NR	PR	48	N		
35	G	5.0		1.4	2.0	2	1	0	0	0	NR	PR	24	N		
36	B	6.0	3.91	3.1	5.0	0	0	0	0	0	PR	CR	15	Y	11	1
37	GK	9.0		4.0	2.0	2	2	1	1	0	NR	NR	26	N		
38	P	3.6	3.39	4.3	4.0	0	0	0	0	0	CR	CR	36	Y	12	0
39	R	3.0	3.07	2.6	2.0	0	0	0	0	0	CR	CR	12	N		
40	R	2.0	5.8	3.1	5.0	0	0	0	0	0	CR	CR	12	N		
41	R	3.0	5.7	3.1	5.0	2	2	2	1	1	NR	NR	12	N		
42	M	5.5	3.46	2.4	3.0	1	1	1	0	0	PR	CR	30	N		
43	PM	4.1	9	7.9	4.0	3	0	0	0	0	CR	CR	12	Y	4	8

Sr. No.	Name	Age (YEARS)	If No, Steroid Dependent Dose	First Relapse (Months after starting Tacrolimus)		No. Of Relapses After Starting Tacrolimus (In 12 Months Peroid)	Sr Creatinine at stopping Tacrolimus	Age (Yrs) after 1yr	Weight (KG) after 1yr	Weight z score after 1yr	Diff Weight Z	Height (CM) after 1yr	HEIGHT z score after 1yr	Diff HEIGHT Z	BMI after 1yr	BMI z score after 1yr	Diff BMI Z
28	AS	2.0	1.46	3	2	3	NOT STOPPED	3.9	20.7	1.9	2.2	110	2.1	6.0	17.1		-3.0
29	SS	3.0	1.14	3	2	5	NOT STOPPED	4.0	18.4	1.0	-0.4	96	-0.9	-0.3	18.8	2.2	-0.1
30	S	10.0	1	3	2	4	NOT STOPPED	11.0	21	-3.8	-1.5	133	-1.6	0.4	11.9	-4.0	-2.7
31	BT	5.3			1		NOT STOPPED	6.0	16	-2.4	-1.0	109	-1.6	0.4	13.5	-2.0	-2.2
32	K	4.4	1	7	3	4	NOT STOPPED	5.5	21	0.5	-0.6	104	-1.7	-0.4	104	2.1	-0.6
33	DJ	5.5	0.3	4	2	2	NOT STOPPED	6.5	17.8	-1.3	-0.6	112	-1.3	0.3	14.2	-0.9	-1.5
34	JS	4.0	0.8	6	2	3	NOT STOPPED	5.0	17.1	-0.6	-0.7	101	-1.7	-0.2	16.8	1.0	-0.6
35	G	5.0	0.7	7	3	1	NOT STOPPED	5.0	20	0.6	-0.4	115	1.3	-0.9	15.1	-0.3	0.5
36	B	6.0		5	2	1	NOT STOPPED	7.5	22.5	-0.6	-0.7	121	-0.7	0.6	15.4	-0.2	-1.7
37	GK	9.0	0.83	5	2	3	NOT STOPPED	10.0	24.2	-1.7	-0.3	127	-1.7	-0.4	15	-1.0	-0.1
38	P	3.6		1	2	1	NOT STOPPED	4.0	16.9	0.3	-0.3	103	0.1	-0.1	15.9	0.9	0.3
39	R	3.0	0.8		1		NOT STOPPED	4.1	14.6	-0.8	0.7	101	-0.3	0.3	14.3	-0.9	0.9
40	R	2.0	1	2	2	1	NOT STOPPED	3.0	13.7	-0.5	1.2	94	-0.5	0.5	15.5	-0.4	0.6
41	R	3.0	1	3	2	1	NOT STOPPED	4.0	14	-1.4	0.4	97	-1.3	-0.4	14.9	-0.7	1.1
42	M	5.5	0.3	4	2	2	NOT STOPPED	6.7	20	-0.7	-0.6	110	-1.9	-0.7	16.5	0.6	-0.4
43	PM	4.1		1	2	1	NOT STOPPED	4.9	15	-1.6	1.2	104	-0.9	1.9	13.9	-1.6	2.2

Sr. No.	Name	Age (YEARS)	OBESITY at 1yr	Short stature at 1yr	Sr Creatinine after 1yr	Sr Albumin after 1yr	RESPONDER/ NON RESPONDER (R / NR)	Treatment Failure (Y/N)	CAUSE OF TREATMENT FAILURE. >/=3 RELAPSES	Recurrence of SR (no response after relapse, after 4 weeks full dose steroids) (Y/N)	Irreversible increase in Sr Creatinine (< 50 ml/min/ 1.73m2) (Y/N)	Tacrolimus Stopped (Y/N)	Reason Of Stopping	Drug Started (Rituximab) (Y/N)	Date Started
28	AS	2.0	N	N	N		NR	Y	Y	Y	N	N	-	Y	03-07-2019
29	SS	3.0	N	N	N		NR	Y	Y	Y	N	N	-	N	-
30	S	10.0	Y	N	N		NR	Y	Y	Y	N	N	-	N	-
31	BT	5.3	Y	N	N		R	N	N	N	N	N	-	N	-
32	K	4.4	N	N	N		NR	Y	Y	N	N	N	-	N	-
33	DJ	5.5	N	N	N		R	N	N	N	N	N	-	N	-
34	JS	4.0	N	N	N		NR	Y	Y	Y	N	N	-	N	-
35	G	5.0	N	N	N		R	N	N	N	N	N	-	N	-
36	B	6.0	N	N	N		R	N	N	N	N	N	-	N	-
37	GK	9.0	N	N	N		NR	Y	Y	N	N	N	-	N	-
38	P	3.6	N	N	N		R	N	N	N	N	N	-	N	-
39	R	3.0	N	N	N		R	N	N	N	N	N	-	N	-
40	R	2.0	N	N	N		R	N	N	N	N	N	-	N	-
41	R	3.0	N	N	N		R	N	N	N	N	N	-	N	-
42	M	5.5	N	N	N		R	N	N	N	N	N	-	N	-
43	PM	4.1	N	N	N		R	N	N	N	N	N	-	N	-

Sr. No.	Name	Age (YEARS)	Response At 6 Months Post Rituximab (CR/PR/NR	serum albumin 0	S Albumin 1	S Albumin 6	S Albumin 12	Diff S Albumin 1	Diff S Albumin 6	Diff S Albumin 12	s.creat 0 M	s.creat 1 M	S CREAT 6 M	S CREAT 12M	Diff s.creat 1 M	Diff S CREAT 6 M	Diff S CREAT 12M
28	AS	2.0	CR	1.37	2.4	2.56	2.5	1.03	1.19	1.13	0.31	0.33	0.41	0.29	0.02	0.1	-0.02
29	SS	3.0	-	1.72	2.17	2.63	2.1	0.45	0.91	0.38	0.21	0.22	0.15	0.3	0.01	-0.06	0.09
30	S	10.0	-	1.56	2.56	2.88	2.3	1	1.32	0.74	0.33	0.34	0.38	0.4	0.01	0.05	0.07
31	BT	5.3	-	1.26	3.56	3.8	3.8	2.3	2.54	2.54	0.28	0.28	0.31	0.2	0	0.03	-0.08
32	K	4.4	-	1.88	4.5	4.2	2.3	2.62	2.32	0.42	0.21	0.2	0.3	0.18	-0.01	0.09	-0.03
33	DJ	5.5	-	1.99	2.1	2.23	2.2	0.11	0.24	0.21	0.42	0.4	0.31	0.18	-0.02	-0.11	-0.24
34	JS	4.0	-	1.5	1.9	1.4	2.7	0.4	-0.1	1.2	0.41	0.4	0.2	0.3	-0.01	-0.21	-0.11
35	G	5.0	-	1.9	2.2	3.1	2.6	0.3	1.2	0.7	0.8	0.9	0.3	0.46	0.1	-0.5	-0.34
36	B	6.0	-	1.68	2.56	2.84	3.8	0.88	1.16	2.12	0.33	0.3	0.34	0.4	-0.03	0.01	0.07
37	GK	9.0	-	2	1.99	2.24	2.3	-0.01	0.24	0.3	0.31	0.3	0.4	0.1	-0.01	0.09	-0.21
38	P	3.6	-	1.26	3.1	2.9	3.1	1.84	1.64	1.84	0.62	0.63	0.48	0.5	0.01	-0.14	-0.12
39	R	3.0	-	1.88	3.1	3.4	3.6	1.22	1.52	1.72	0.41	0.4	0.38	0.22	-0.01	-0.03	-0.19
40	R	2.0	-	1.5	3.2	3.1	3.4	1.7	1.6	1.9	0.11	0.1	0.43	0.42	-0.01	0.32	0.31
41	R	3.0	-	2	2.6	2.7	2.1	0.6	0.7	0.1	0.3	0.3	0.28	0.32	0	-0.02	0.02
42	M	5.5	-	1.35	2.67	3.12	3.8	1.32	1.77	2.45	0.32	0.35	0.29	0.19	0.03	-0.03	-0.13
43	PM	4.1	-	1.9	2.34	2.8	3.8	0.44	0.9	1.9	0.29	0.3	0.46	0.38	0.01	0.17	0.09

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The Principal,
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Subject: **Approval of Plan of Thesis.**

This is to inform you that the Faculty of Medical Sciences in its meeting held on 29.10.2021 has approved the plan of thesis of **Shubham Dutta**, a student of your college for **MD Paediatrics** along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis

Efficacy of tacrolimus in children with steroid-dependent (sdns) and steroid-resistant nephrotic syndrome (srns).

Supervisor
Dr. Gurdeep Singh Dhooria
Assoc. Prof.,
Dept. of Paediatrics,
DMCH, Ludhiana.

Co-Supervisor

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The student has to submit the four copies of thesis (along with PDF format) , to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She must directed to attach a photocopy of this letter with the forwarding letter while submitting thesis to the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic,(if any).

Dr. S P Singh MS(Oph)
Controller of Examinations

Note :

91. *If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.*
92. *The student may submit the thesis as per the schedule already conveyed i.e for May/June examination 30th Nov of the preceding the year of examination and for Nov/Dec examinations 31st May of the year of examination.*

EFFICACY OF TACROLIMUS IN CHILDREN WITH STEROID-DEPENDENT (SDNS) AND STEROID-RESISTANT NEPHROTIC SYNDROME (SRNS)

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED IN

PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

MD

In

PAEDIATRICS

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES

FARIDKOT

MARCH, 2021

DR. SHUBHAM DUTTA

DEPARTMENT OF PAEDIATRICS
DAYANAND MEDICAL COLLEGE AND HOSPITAL
LUDHIANA

ABSTRACT OF PLAN OF THESIS

Title	Efficacy of Tacrolimus in children with Steroid-Dependent (SDNS) and Steroid-Resistant Nephrotic Syndrome (SRNS)
For the degree of	MD (Paediatrics)
Name of the candidate	Dr. Shubham Dutta
Supervisor	Dr Gurdeep Singh Dhooria, Associate Professor, Department of Pediatrics, DMCH, Ludhiana
Co-supervisors	Dr. Deepak Bhat, Professor, Department of Pediatrics DMCH, Ludhiana
Institution	Dayanand Medical College & Hospital, Ludhiana
University	Baba Farid University of Health Sciences, Faridkot

INTRODUCTION: Nephrotic syndrome(NS) usually begins between the age of 2 and 5 years. It is characterized by proteinuria, hypoalbuminemia, hyperlipidaemia and edema. Idiopathic nephrotic syndrome (INS) is the most frequent form of NS in children representing 90% of cases between 1 and 10 years. Majority of patient with minimal change disease, more than 90% respond to long term steroid therapy. Remission is usually achieved with in two weeks. Children not responsive to steroid are considered as SRNS while, children that relapse after lowering dose or stopping steroid are considered as SDNS. Immunosuppressant drugs such as Cyclophosphamide and Cyclosporine-A have been used in patients not responding to steroid alone. However, drugs like Cyclosporine-A have high relapse rate and high resistant rate. CNIs(Calcineurin inhibitors) such as tacrolimus is a better alternative with better safety profile and a higher remission and low relapse rate.

AIM OF STUDY: 1) To Study the efficacy of Tacrolimus in children with Steroid-Dependent (SDNS) and Steroid-Resistant Nephrotic Syndrome (SRNS).
2) To study the safety of Tacrolimus

MATERIALS & METHODS: This is a Prospective, non-interventional, Observation study to be conducted in Paediatric Nephrology Clinic of DMCH Ludhiana. Children of Steroid-Dependant (SDNS) and Steroid-Resistant Nephrotic Syndrome (SRNS) between 3 months to 18 years of age who have received Tacrolimus earlier or are currently on treatment and are being followed up for at least 1 year in the clinic will be included

CLINICAL SIGNIFICANCE: The treatment of complex, corticosteroid-resistant NS continues to be a difficult challenge. Patients receiving tacrolimus showed lower relapse rate. Therapy with tacrolimus can be considered a reasonable alternative to cyclosporine-A (CsA) for patients with idiopathic SRNS. In the region of Punjab, there are very few studies done on the subject and this study evaluates the result of tacrolimus treatment in context of efficacy, adverse effects in children with idiopathic SRNS and SDNS in Punjab.

KEYWORDS: Idiopathic Steroid-Resistant Nephrotic Syndrome (SRNS), Steroid-Dependent Nephrotic Syndrome (SDNS), Difficult Nephrotic Syndrome, Tacrolimus

(Signature) Candidate

(Signature) Co-supervisor

(Signature) Supervisor

(Signature) Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"EFFICACY OF TACROLIMUS IN CHILDREN WITH STEROID-DEPENDENT (SDNS) AND STEROID-RESISTANT NEPHROTIC SYNDROME (SRNS)"** exist in the Department of Paediatrics, DMC&H, Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis is genuine and is collected by the candidate himself under our supervision and guidance.

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Date : _____

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BY
RESEARCH & ETHICAL COMMITTEE
DAYANAND MEDICAL COLLEGE & HOSPITAL, LUDHIANA

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Department	Paediatrics
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Likely date of appearing in PG examination	May, 2023
Date of enrollment	30th June, 2020
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Approved: Yes / ~~No~~

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4	DATE OF ADMISSION OF COURSE	30th June, 2020
5	TITLE OF THE TOPIC	Efficacy of tacrolimus in children with Steroid-Dependant (SDNS) and Steroid-Resistant Nephrotic Syndrome (SRNS)

6. BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

In terms of glomerular disease in childhood, Nephrotic syndrome is the most frequently occurring one. NS usually begins between the age of 2 and 5 years. It is characterized by proteinuria, hypoalbuminemia, hyperlipidaemia and edema. Idiopathic nephrotic syndrome (INS) is the most frequent form of Nephrotic syndrome in children representing more than 90% of cases between 1 and 10 years of age and 50 percent after 10 years of age.[1]

Majority of patient with minimal change disease, more than 90% respond to long term steroid therapy. However, 50% of mesangial proliferation and 30% of focal segmental glomerulosclerosis response to steroid therapy.[2] Most of the children respond very well to steroid treatment. Remission is usually achieved with in two weeks. Most children will have at least one relapse or recurrence of protein in the urine. Around 10% of children have secondary nephrotic syndrome with significant lesions. Some children do not respond to steroid and are considered as SRNS while some children relapse after lowering dose or stopping steroid and considered as SDNS. In practice immunosuppressant drugs such as Cyclophosphamide and Cyclosporine-A has been used as a drug in patients who do not respond with steroid alone. However these immune- suppressant drugs like Cyclosporine-A have high relapse rate and high resistant rate.[3] CNIs(Calcineurin inhibitors) such as tacrolimus can be a better alternative drug with better safety profile and a higher remission and low relapse rate.[4]

Patients achieving complete remission (urinary protein-creatinine ratio < 0.2 g/g and serum albumin ≥ 2.5 g/dL) or partial remission (urinary protein-creatinine ratio, 0.2 to 2 g/g, and serum albumin ≥ 2.5 g/dL) at 6 and 12 months; time to remission; number of relapses and side effects.[5]

NS is a chronic disease that has numerous associated comorbid conditions. The treatment of complex, corticosteroid-resistant NS

continues to be a difficult challenge.[5] Patients receiving tacrolimus showed lower relapse rates, decreased blood levels of cholesterol, and lack of cosmetic side effects, these were secondary end points. Although therapy with tacrolimus might be considered a reasonable alternative to cyclosporine-A (CsA) for patients with idiopathic SRNS.

Tacrolimus (TAC) is a macrolide immunosuppressant which inhibits calcineurin and completely blocks the translocation of the cytosolic component of the nuclear factor of activated T cells (NF-AT).[6]

In a study by Becknell B et al. concluded Tacrolimus having superiority over cyclophosphamide and give further evidence that in childhood SRNS are both easy and vital for improving the standard of care.[7]

The main goal of treatment is complete or partial remission of proteinuria, which is the most important marker of long term outcome. Calcineurin inhibitors (CNIs) are used to avoid steroid toxicity in children with NS. There are data on the relative efficacy and safety of calcineurin inhibitors and alkylating agents for NS in children. There are different immunosuppressant drugs but tacrolimus can be used in the treatment of childhood NS which is less expensive, have less cosmetic side effects and easy to administered.[8] Studies on tacrolimus have shown safety and efficacy of tacrolimus, a drug which can be administered orally as a twice daily dose in the management of childhood NS like case reports [9-11] and a randomized controlled trial (RCT)[5] with only 17 out of 41 SRNS patients being CYC-SRNS (cyclophosphamide) patients. There are no studies on efficacy of CNI (Calcineurin inhibitors) in our Region. Hence, need to study of efficacy of Tacrolimus in children with steroid dependant and steroid resistant Nephrotic Syndrome is required.

6.2 REVIEW OF LITERATURE

In accordance with the literature, Tacrolimus in a RCT trial by Choudhary et al In a tertiary-care hospital, 41 consecutive patients with idiopathic SRNS, estimated glomerular filtration rate greater than 60 mL/min/1.73 m2, and histological characteristics showing minimal change disease, focal segmental glomerulosclerosis, or mesangioproliferative glomerulonephritis were randomly assigned to treatment with tacrolimus (n = 21) or CsA (n = 20). Tacrolimus (0.1 to 0.2 mg/kg/d) or CsA (5 to 6 mg/kg/d) was given for 1 year, cotreatment with alternate-day prednisolone and enalapril.

Tacrolimus or CsA in combination with low-dose steroids show similar efficacy in inducing remission in patients with SRNS. Therapy with tacrolimus is a promising alternative to CsA in view of the lower risk of relapses and lack of cosmetic side effects.[5]

Another study at AIIMS Delhi by Following six months of therapy with tacrolimus, patients with complete or partial remission were randomly assigned such that 29 received MMF while 31 received tacrolimus along with tapering prednisolone on alternate days for 12 months. The proportion of patients with a favorable outcome (sustained remission, infrequent relapses) at one year was significantly lower (44.8%) in the MMF group than in the tacrolimus group (90.3%). The incidence of relapses was significantly higher for patients treated with MMF than tacrolimus (mean difference: 1.05 relapses per person-year). While there was no difference in the proportion of patients with sustained remission, the risk of recurrence of steroid resistance was significantly higher for patients receiving MMF compared to tacrolimus (mean difference: 20.7%). Compared to tacrolimus, patients receiving MMF had a significantly (71%) lower likelihood of a favorable outcome and significantly increased risk of treatment failure (frequent relapses, steroid resistance). Thus, replacing tacrolimus with MMF after six months of tacrolimus therapy for steroid-resistant nephrotic syndrome in children is associated with significant risk of frequent relapses or recurrence of resistance concluding tacrolimus to be superior to

mycophenolate mofetil in sustaining remission in children with idiopathic steroid resistant nephrotic syndrome.[12]

Another study Becknell B et al. suggested tacrolimus to have better results in steroid resistant cases.[13]

A retrospective chart reviews of 18 children, received prednisolone at the start of tacrolimus. 72.2% children achieved complete response (CR), medicine was well tolerated and treatment was effective.[14]

A clinical study suggest that the low dose tacrolimus and prednisone for 6 months, can achieved complete remission in 96.66% and partial remission in 3.33%. Over 85% of the patients achieved reduction in proteinuria, serum albumin improvement and serum lipid recovery which indicates tacrolimus can be considered as alternative to other immuno- suppressive drugs.[15]

Tacrolimus, a calcineurin inhibitor that inhibits interleukin-2-driven T-cell activation, has shown promising results in various single-cantered studies.[9,10,16,17]

Loeffler et al. [9] reported the use of tacrolimus in seven children with SRNS; six children achieved CR and one went into PR after a mean duration of 2 months of therapy. Five of the seven children were off steroids on follow-up, although the steroid-free duration was quite short.

Some study suggest that tacrolimus is well tolerated by the children. There are only few adverse effect reported. The most common side effects were diarrhea and hyperglycemia induced by tacrolimus treatment.[16,18] Tacrolimus induced HUS were seen with tacrolimus therapy within one month but improved after 2 weeks of stopping tacrolimus.[19] Insulin dependent diabetes mellitus were observed in some children diagnosed with SDNS.[20] Rarely children have new onset hypertension, seizure and sepsis.[9,10] Nephrotoxicity were observed in SRNS but was reversible.[9] Urinary tract infection and pneumonia are the major side effects observed but reported cases are very low. Other non-specific symptoms like body aches, flu symptoms, sores in your mouth and throat are observed. All of the symptoms are mild and can be controlled.

In a prospective non-randomized, non-controlled study by Chen, HX., Cheng, Q., Li, F. *et al.*, Chinese children with SRNS who failed the previous full-dose prednisone treatment were given tacrolimus (0.1 mg/kg/day) and low-dose prednisone (0.25–0.50 mg/kg/day) and compared the overall remission rate (ORR) and adverse events in the follow-up period with this therapeutic regimen. A total of 76 children were enrolled into the study with an average follow-up period of 18 ± 6 months (maximum 36 months). ORR achieved by the first, third, and sixth months was 94.7%, 94.7%, and 96.0%, respectively. All patients who attained an initial tacrolimus trough concentration ($FK506C_0$) > 6 ng/mL (60.3%) achieved remission. The relative risk of relapse at $FK506C_0$ < 3 ng/mL compared to 3–6 ng/mL, 6–9 ng/mL, and 9–12 ng/mL was 2.3, 3.2, and 16.9, respectively. During the follow-up period, adverse effects that had been previously reported were rare.[21]

The study based in efficacy of tacrolimus in children with steroid resistant and steroid dependent nephrotic syndrome in our region is lacking.

6.3 AIMS AND OBJECTIVES OF THE STUDY

- Study the efficacy of tacrolimus in children with Steroid-Resistant (SRNS), Steroid-Dependent Nephrotic Syndrome (SDNS)
- To study the safety of Tacrolimus.

7. MATERIALS AND METHODS

Design - Prospective, Non Interventional, Observation study.

Setting – Paediatric Nephrology Clinic of a tertiary care hospital, DMCH Ludhiana

7.1 Source of Data

Source of data will be Patients of Steroid dependant or Steroid resistant NS between 3 months to 18 years of age who have received tacrolimus earlier and are being followed up for at least 1 year in the Paediatric Nephrology Clinic in department of Pediatrics, DMCH, Ludhiana.

7.2 METHOD OF COLLECTION OF DATA

INCLUSION CRITERIA

1. All Patients of Steroid dependant or Steroid resistant nephrotic syndrome
2. between 3 months to 18 years of age who have received tacrolimus with
3. follow up of at least 1 year in Paediatric Nephrology Clinic of the department of Pediatrics, DMCH.

EXCLUSION CRITERIA

- Patients of congenital Nephrotic syndrome (age at onset <3 months)
- Patients with nephrotic syndrome due to secondary causes.
- History of diabetes mellitus or liver disease
- If attendants refused to give consent for participation in the study.
- Follow up less than 1 year.

CONSENT

Written consent will be obtained from the attendants of the children. Patients will be assessed appropriately and data will be collected on specified patient proforma including information such as age, sex, dates of starting Tacrolimus, time to remission, duration of remission, no. of relapses, weight, BMI, side effects.

Status of patients will be defined according to the following categories

Remission- Urine albumin nil or trace (or proteinuria <4 mg/m2/h) for 3 consecutive early morning specimens

Relapse- Urine albumin 3+ or 4+ (or proteinuria >40 mg/m2/h) for 3 consecutive early morning specimens, having been in remission previously.

Sustained remission- No relapse for 1 year

Frequent relapsers- Two or more relapses in initial six months or more than three relapses in any twelve months.

Infrequent Relapsers -Patients who have three or less relapses a year

Steroid dependence - Two consecutive relapses when on alternate day steroids or within 14 days of its discontinuation.

Steroid resistance- Absence of remission despite therapy with daily prednisolone at a dose of 2 mg/kg per day for 4 weeks.

Classification of Response-

Responder, Patient who are in Complete remission/ Partial remission at 6 month of treatment.

Non Responder, Patient showing no response to treatment.

Complete remission, Partial Resistance, No Response and Treatment Failure

Complete remission defined as the absence of proteinuria (Up/Uc ratio <0.2 g/g) and serum albumin level of 2.5 g/dL or greater;

Partial remission, as non- nephrotic proteinuria (Up/Uc ratio of 0.2 to 2.0 g/g) and serum albumin level of 2.5 g/dL or greater;

Nonresponse as persistent nephrotic-range proteinuria (Up/Uc ratio >2 g/g) or hypoalbuminemia with albumin less than 2.5 g/dL.

Treatment failure, defined in patients showing nonresponse despite 6 months of treatment, 3 or more relapses in 12 months while on treatment, persistent nephrotoxicity, or death.

It will be a observational hospital based study of patients of SRNS and SDNS who were treated with tacrolimus at least for 1 year or being treated with tacrolimus and having a follow up of at least 1 year in

Paediatric Nephrology Clinic in the department of pediatrics of DMC&H, Ludhiana.

Written consent will be obtained from the attendants of the children. Patients will be assessed appropriately and data will be collected on specified patient proforma including information such as age, sex, dates of starting Tacrolimus, time to remission, duration of remission, no. of relapses, weight, BMI, side effects.

OUTCOME

Primary outcome -The primary end point is the proportion of patients achieving complete or partial remission at the end of 6 months of therapy.

Secondary outcome include time to achieve remission, proportion of participants in remission at 12 months, frequency of relapses, and side effects

STATISTICAL ANALYSIS

Analysis will be done by SPSS 21.0 (Statistical Product and Service Solutions Chicago 21.0 version) Continuous data are presented as mean, 95% confidence interval (CI), and range unless other- wise stated.

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

No

7.4 HAS ETHICAL CLEARANCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

Attached herewith

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PROFORMA

Tacrolimus File Record

S. No.

Name: Age:

Sex: Urban/Rural:

Ped Nephro File No: MRD No: Cr No:

Diagnosis: FRNS/SDNS/SRNS

Steroid Resistant: Late / Early

Date of birth:

Age Of Onset(Year / Month):

Hypertension at onset:

Haematuria at onset:

If SDNS: Dependent Dose (Mg/Kg/Day):

No Of Relapse Last One Year (Before Tacrolimus):

Prior Immunosuppressives:

1)Levamisole: Y/N

2)Cyclophosphamide :Y/N

3) Mycophenolate: Y/N

4) Cyclosporin: Y/N

Status Of Patient At Start Of Tacrolimus: CR / PR / NR

Steroid Toxicty: Cataract/ Cushingoid / Short Stature/ Overweight/ Obesity/ Behavior abnormality

Renal Biopsy Findings(Year):

Signature of candidate **Signature of Supervisor**

Date Of Start Of Tacrolimus_____

Age At Start Of Tacrolimus:

Duration Of NS (yrs, months): (Age of onset of NS MINUS Age of start of Tacrolimus)*

Age YRS	Weight KG	Height CM	BMI	Sr Creatinine	Sr Albumin
Z SCORE					

Baseline Investigation: Cbc:

RFT,

OT,PT

S.Albumin,

S.Cholesterol

Urine PCR

Dose Given: _____ Mg/Kg

Associated Medications:

Side effects of Tacrolimus: (Tick)

Hypertension	Reversible Nephropathy
Hyperkalemia	Hypertrichosis
Seizure	Gingival hyperplasia
Increase Blood Sugar	Acne
Increase OT/ PT	Skin infections
Diarrhea	Major infection (Requiring hospitalization)Diagnosis
UTI	Others

Signature of candidate **Signature of Supervisor**

Date/ Months	URINE PCR	Sr Creatinine	Sr Albumin	Cholesterol	Electrolytes	OT/PT	TACROLIMUS LEVELS	Edema
1								
3								
6								
9								
12								
15								
18 months								

Results

Status Of Patients At 6 Months Post Tacrolimus: CR / PR/ NR

Status Of Patients At 12 Months Post Tacrolimus: CR / PR/ NR

Status Of Patients At 18 Months Post Tacrolimus: CR / PR/ NR

Tacrolimus Given For Duration (Months):

Off Steroids: Y/N_____ (IN SDNS/ FRNS)

If Yes, Duration Off Steroids: _____

If No, Steroid Dependant Dose: _____

First Relapse (Months after starting Tacrolimus):

No. Of Relapses After Starting Tacrolimus (In 12 Months Peroid):

Sr Creatinine at stopping Tacrolimus:

Signature of candidate **Signature of Supervisor**

PARAMETERS AFTER ONE YEAR OF TACROLIMUS

Age YRS	Weight KG	Height CM	BMI	Sr Creatinine	Sr Albumin	Urine PCR
Z SCORE						

Treatment failure: **Y/N**

CAUSE OF TREATMENT FAILURE

Recurrence of SR (no response after relapse, after 4 weeks full dose steroids) y/n

FR ≥ 3 relapses in one year y/n

Irreversible increase in Sr Creatinine (< 50 ml/min/ 1.73m2) y/n

Tacrolimus Stopped: Y/N

Reason Of Stopping_____

Drug Started: Rituximab_____Date_____

Response At 6 Months Post Rituximab: Cr / Pr / Nr

Signature of candidate **Signature of Supervisor**

Patient Monitoring Chart

Date	Weight/ Height	Blood Pressure	Swelling	Infection	Urine Albumin	Medications

Signature of candidate **Signature of Supervisor**

PATIENT'S PARENT/GUARDIAN CONSENT FORM

Date: ____/____/____

I .....F/o, M/o ..... R/o ..... am willing to let my child participate in the study entitled Bed **"EFFICACY OF TACROLIMUS IN CHILDREN WITH STEROID-DEPENDENT (SDNS) AND STEROID-RESISTANT NEPHROTIC SYNDROME (SRNS)"**. The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason. This will not affect my treatment and investigation of my child.

Signature of the Witness
Name:

Signature/Thumb Impression of guardian
Name:

Signature of the Supervisor

Signature of Candidate

ਮਰੀਜ ਦੇ ਮਾਤਾ/ਪਿਤਾ ਦਾ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ __/___/____

ਮੈਂ _____ ਪਿਤਾ/ਮਾਤਾ _____,

ਵਾਸੀ _____

ਆਪਣੇ ਬੱਚੇ ਦੇ ਇਸ ਅਧਿਐਨ ਵਿੱਚ ਹਿੱਸਾ ਲੈਣ ਤੇ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿੱਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈਂ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈਂ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ/ਚਾਹੁੰਦੀ ਹਾਂ ਕਿ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂੰ ਕਿਸੇ ਵੀ ਤਰ੍ਹਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀਂ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂੰ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂੰ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂੰ ਇਸ ਖੋਜ ਵਿੱਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆਂ ਹੈ ਅਤੇ ਮੈਨੂੰ ਇਹ ਯਕੀਨ ਹੈ ਕਿ ਇਹ ਖਤਰਾ ਬਹੁਤਾ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂੰ ਇਸ ਖੋਜ ਕੰਮ ਵਿੱਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ-ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈਂ ਇਸ ਖੋਜ ਕੰਮ ਵਿੱਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇਂ ਵਾਪਸ ਲੈ ਸਕਦਾ/ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਬੱਚੇ ਦੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀਂ ਹੋਵੇਗਾ।

_____ _____

ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ _____ ਮਿਤੀ _____

ਪਤਾ _____ ਪਤਾ _____

_____ _____

ਨਰੀਖਕ ਦੇ ਹਸਤਾਖਰ ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ

मरीज के माता/पिता का अनुमति फार्म

तिथि ___/___/___

मैं _____ पिता/माता/_____ वासी _____, अपने बच्चे के इस शोधकार्य में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ कि स्वीकृत देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है कि यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामूली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे बच्चे के इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____
गवाह के हस्ताक्षर

_____
मरीज के माता/पिता के हस्ताक्षर

तिथि _____

पता _____

_____

_____

_____
नरीक्षक के हस्ताक्षर

_____
प्रत्याक्षी के हस्ताक्षर